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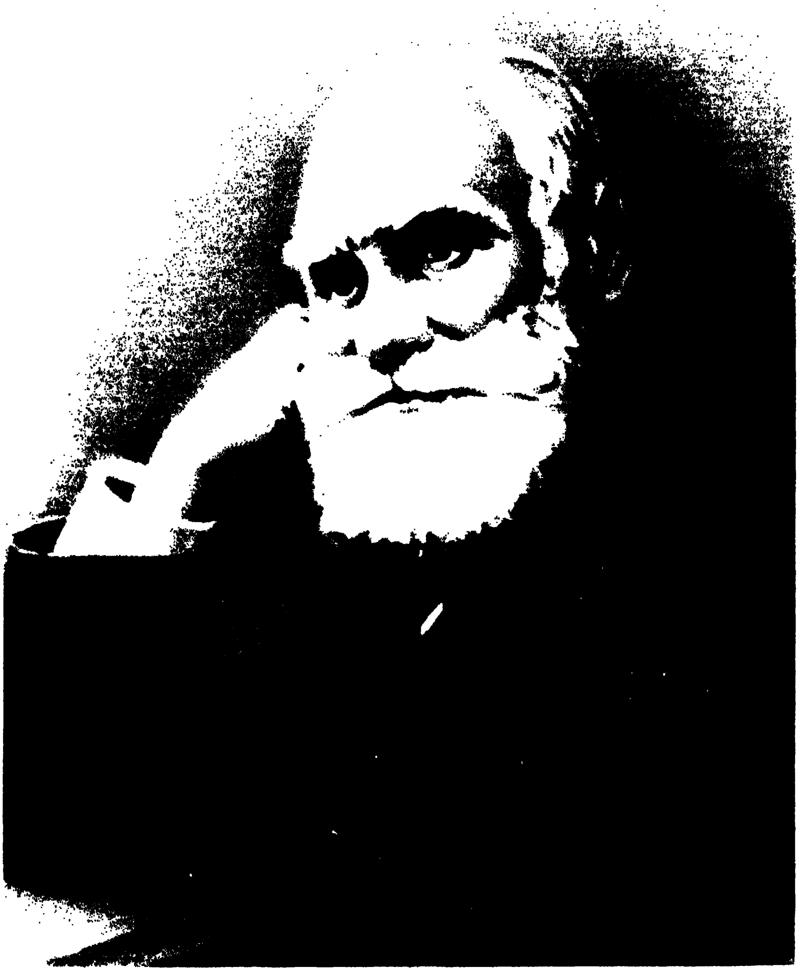

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TEXT-BOOK OF PHYSIOLOGY

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Translated from the Russian
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PREFACE

The first edition of this text-book of physiology appeared in 1939. It was reprinted in the difficult war years, while in 1951-53 much of it was rewritten. For the present edition some parts have been abridged and a number of changes and additions made.

In preparing this text-book, the authors sought to reflect as fully as possible all the fundamentally new ideas introduced into physiology by I. P. Pavlov, our teacher and renowned naturalist. Pavlov paved the way for an understanding of the physiological processes in an integral, normal organism that is in natural contact with the external environment. This was achieved by Pavlov not only by introducing and systematically applying his absolutely novel methods of research. Of still greater importance in the creation of a new physiology—the physiology of an integral organism—was Pavlov's new principle of investigation; this required that all phenomena in an organism be studied in their dependence on the nervous system which through reflexes establishes all the connections of the animal organism with surrounding nature. Precisely this principle underlies Pavlov's great teaching on conditioned reflexes, which extended the principle of scientific determinism to a comprehension of the most intricate phenomena in the world—a knowledge of all forms of activity of the higher parts of the brain, including consciousness.

From this it follows (and we have endeavoured to show it) that the integrating activity of the nervous system, in the true sense of the word, can be understood only if we examine the nervous activity in its entirety as based on the reflex mechanism, in the new, Pavlovian concept. Normally each reflex act is an indissoluble union of conditioned and unconditioned reflexes; these reflex acts determine the character and course of all physiological processes which depend on the concrete conditions of the existence of animals and of man's activity.

Such are the fundamental principles which we have tried, within the limits of available factual material, to reflect in this book. The authors realize that so far they have not fully coped with their task. However, their attempt is justified if only by the fact that even an outline of the significance of the principles underlying Pavlov's teaching may in a certain measure help to disseminate them.

Speaking of the prospects of his research, Pavlov said that when he expounds his work he "fervidly dreams of the possibilities, majestic and ever-growing, which would open up before our science, and of the boundless influence this science would have on human nature and human destiny." This "boundless influence" of physiology that Pavlov mentions must serve only lofty purposes. Our science is aimed at improving the health of people, at delivering them from physical suffering during illness. It contributes to a wise organization of labour, leisure and nourishment; it helps to conquer inaccessible heights, to penetrate the depths of the oceans; it strives to make known the laws which govern the behaviour of the human body. The authors offer this book to foreign students and physicians in the hope that thereby they will make their modest contribution to the international scientific ties which serve the cause of peace and progress.

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PART 1

FUNDAMENTAL CONCEPTS OF PHYSIOLOGY

CHAPTER 1

THE SUBJECT AND BRIEF HISTORY OF PHYSIOLOGY

The Subject and Branches of Physiology

The physiology of man and animals is the study of the functions of human and animal organisms in their interaction with the environment. To make the vital activity of the organism known, physiology must define the significance of its various functions, the interconnection of these functions and their dependence on external and internal conditions. Analyses of particular functions of the organism must be subordinated to the task of understanding the vital activity of the organism as a whole in different conditions of its existence (synthetic study). Synthetic physiology, elaborated on the basis of Pavlov's teaching, is what can lead to a deeper study of the functions of the organism and to learning to control them.

As the principal branch of biological sciences, human physiology is closely connected with a number of other branches of science. It is, above all, indissolubly linked with morphological sciences—anatomy and histology—which treat of the structure of tissues and organs performing various functions of the organism. At the same time when the human organism is studied physiologically, the particular significance that social conditions and social labour have for man must always be borne in mind.

Physics and chemistry are of great importance for the advance of physiological knowledge. Since the fundamental task of physiology is to study the processes developing in the organism, it is highly essential to know the physical and chemical laws underlying each physiological function. However, physiological phenomena possess definite qualitative features. Though based on physical and chemical laws, they cannot be said to be totally governed by them, since they are subject to biological laws arising in the course of evolution.

The branch of physiology which studies chemical processes in the organism has become an independent science—biochemistry—but it has preserved a very close connection with physiology.

As a branch of science, physiology has been engendered by the requirements of practice and, primarily, of medicine. Hence its bond with clinical medicine. Clinical practice has substantiated and corroborated a number of physiological propositions. Some phenomena observed in the clinic, such as the disappearance or derangement of functions of certain organs (for example, of the endocrine glands), pathological disturbances of respiration, blood circulation, etc., help to establish the physiological significance of this or that system or organ. As stated by Pavlov, clinical phenomena in man represent experiments performed by life, as it were, which cannot be reproduced in a laboratory because no human being can be subjected to experiments that may entail unhappy consequences.

To ensure a thorough study of the functions both of human and animal organisms, physiology has, in the course of its growth as a broad sphere of biological knowledge, created its branches with different methods, objects of investigation and practical aims.

Physiology has developed mainly on the basis of a study of higher animals and human beings, and, therefore, the facts accumulated by it relate predominantly to the organism of mammals, most often of laboratory animals such as dogs, cats, rabbits, guinea-pigs, rats and mice (of the lower vertebrates, the frog was the most important object of experimentation). With the rise of the evolutionary theory, the investigation of physiological phenomena at different stages of development of the animal kingdom acquired great importance and gave birth to comparative (or evolutionary) physiology which studies physiological processes in their phylogenetic development in various species of invertebrates and vertebrates. Closely allied with it is the chapter of physiology which studies the development of functions in the ontogenesis.

From a broad biological aspect, the problems relating to the influence of environment on the organism of animals are studied by oecological physiology. This branch of physiology deals with the peculiarities of physiological processes in various species of animals depending on the different conditions of their existence. These conditions are determined by the physical and chemical features of the environment, the nature of the surrounding locality, climatic factors, as well as by the activities peculiar to animals of the given species. With some corrections, which are always indispensable when dealing with data pertaining to animals, the material provided by oecological physiology is important for human physiology as well, particularly for a direct study of the action of the external environment on man.

In its progress, physiological science has provided a foundation for a number of physiological branches which are of great practical importance. One of these is the physiology of agricultural animals.

The elaboration of certain problems of clinical medicine has resulted in the creation of clinical physiology,* which embraces numerous problems relating to the fundamental tasks of clinical practice. Particularly great progress has been achieved in solving problems elaborated by Pavlov and relating to the clinical physiology of digestion, nervous activity and its regulating influence on all processes in the body. Success has also been achieved in the work on problems connected with the clinical physiology of internal secretion, blood circulation, respiration, excretion and metabolism. The study of the physiology of a diseased organism is at the same time a practical school of natural-scientific thought. It is not by accident that the biggest physiological institutes of the Soviet Union, the United States and other countries are bound up with clinics.

The Rise of Physiology

Physiology arose from the requirements of medicine, whose leading representatives already in ancient times realized that it is impossible to treat a human being without knowing the structure of his body and the functions of its organs. The physicians and thinkers of ancient Greece and Rome** tried to obtain an idea of the activity of various organs of the body, but their conclusions were based almost entirely on speculative reasoning resulting mainly from a study of the rough structure of these organs.

With the change in social and economic relations in Western Europe in the period of the rise and development of capitalism, natural sciences developed rapidly: Copernicus established that the earth revolves round the sun and laid the foundations of modern astronomy: Newton formulated the fundamental principles of mechanics and the law of gravitation; Vesalius correctly described some specific features in the structure of the human body which had been erroneously interpreted by ancient anatomists; Bacon proclaimed that knowledge is true only when it is based on experience; Descartes tried to explain both the movement of the heavenly bodies and the behaviour of animals by the laws of mechanics.

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* The demarcation line between clinical and pathological physiology is very relative. Pathological physiology studies mainly the general mechanisms of the disturbances of the physiological processes (that is why it can base itself largely on experiments with animals). Clinical physiology, meanwhile, investigates the disturbances that occur in various functions of the human organism during certain diseases; essentially this is pathological physiology, which is concerned mainly with investigating particular pathological phenomena in man.

** The authors do not refer in this text-book to data relating to the rise and development of physiology in India and China, since that question has not been sufficiently studied by them.

In the same period—"300 years ago, in conditions of profound obscurantism and inconceivable confusion which at that time were characteristic of the approach towards the activity of the human and animal organisms, but which were sanctified by the irreproachable authority of the classical scientific legacy—the physician William Harvey discovered one of the most important functions of the organism—blood circulation, and thereby laid the foundation of a new branch of exact human knowledge—animal physiology."*

The year 1628, when Harvey discovered blood circulation, is regarded as the date of the foundation of physiology not only because one of the most essential functions of the organism was investigated for the first time Harvey's introduction of vivisection into scientific practice made the discovery of blood circulation possible. With this method, incisions made in the skin coverings and tissues make it possible to expose the organs of animals and thus directly observe their functions. Harvey's extensive experiments with physiological processes carried out under special conditions were aimed at probing and ascertaining the factors which determined them.

The Development of Physiology in the Pre-Pavlovian Period

In the 17th, 18th and almost the entire first half of the 19th century physiological knowledge advanced rather slowly, but some of the discoveries made at that period provided the foundation for its further development.

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* I. Pavlov, *Complete Works*, Vol. VI, p. 425. (Preface to the Russian translation of W. Harvey's book, Moscow-Leningrad, 1927.)

References throughout the book are to Russian editions.

In 1661, Malpighi discovered the capillaries; blood pressure in the arteries was measured for the first time (St. Hales, 1732); Bernoulli's researches into the movement of fluids (1738) laid the foundation for future haemodynamics; Borelli gave the first scientific description of the movements of the thorax during the respiratory act, as well as of the kinematics of the skeleto-muscular levers; Réaumur and Spallanzani (1777) discovered the properties of gastric juice. In the 18th century, Whytt made a discovery which later underlay the formation of the reflex theory; he showed that after the destruction of the spinal cord, a frog no longer responds with a motor reaction when its extremity is pinched (Chapter 51).

The most important achievement of physiology in the 18th century was the application of the laws of inanimate nature, the laws of chemistry, to processes developing in a living organism.

In the forties of the 18th century, Mikhail Lomonosov discovered the law of constancy of matter and motion, substantiated the kinetic theory of the structure of matter, and proved (1748) that oxidized metals absorb a certain component part of the air; thus he established that air is a mixture of various gases. Thirty years later pure oxygen was isolated, and Lavoisier showed that respiration was, in the final analysis, oxidation of the organic compounds of the body by the oxygen in the air. By measuring the amount of heat produced in the organism as it consumes oxygen, Lavoisier and Laplace demonstrated that the oxidative processes yield the same amount of heat both during the oxidation of "carbonic combinations" in the organism and during their combustion outside the organism.

Owing to this there arose in physiology the notion of respiration as chemical processes of oxidation, and the notion of "animal heat" as of a release of energy determined by the chemical reactions of oxidation. In this way, the connection between the processes in animate and in inanimate nature was established.

The theory of irritability of tissues, and especially of irritability of nerves, was also originated in the 18th century. This was a prerequisite for the formulation by Johannes Müller and Marshall Hall (in the thirties of the 19th century) of their reflex theory, which existed without change prior to Sechenov and Pavlov. In 1812-30 Legallois, Magendie and Flourens began to investigate the role of various parts of the brain and of the spinal cord.

Thus, by the middle of the last century, physiology had accumulated certain facts concerning blood circulation and respiration; it had advanced the notion of reflex and had elaborated methods of access to almost any organ of the body. Physiology was already in a position to make use of scientific data on the microscopic structure of various organs.

Such are, in very brief outline, the results attained by physiology during the first two centuries of its existence. By the second half of the 19th century it was already a developed branch of natural science, whose deductions were based on experimentation. This branch of science already possessed a considerable amount of facts; however, with the exception of data on the role of respiration and blood circulation, these facts were uncoordinated; they were not united by theoretical concepts of interconnection between various functions of the organism.

At the same time, a characteristic feature of the research which was done up to the second half of the 19th century was that all the investigations were carried out by scientists who worked singly, without collaborators, and had no special physiological laboratories. There were almost no physiological apparatuses at that time, the only laboratory equipment being microscopes, a set of simple instruments for vivisection, scales, thermometers and chemical glassware; calorimeters of Lavoisier, pumps and Leyden jars were the most complex instruments of that time. The first manometers and galvanometers appeared in the period between 1820 and 1850. Before the middle of the 19th century physiology had already taken final shape as an independent branch of science, but all of its outstanding representatives were simultaneously practising physicians (Bichat, Magendie, Bell), anatomists and zoologists (Spallanzani, Müller), or physicists and chemists (Boyle, Lavoisier).

In approximately the second half of the 19th century, physiology began to make rapid strides along with all the other exact sciences. This was due to the rapid growth of the productive forces which required the development of exact knowledge of nature and resulted in a considerable extension of natural-scientific research.

Three great discoveries of natural science—the law of conservations of energy, the cellular theory and the theory of evolution—were responsible for the swift progress of all biological sciences in that period. The advance of physics and chemistry armed the researchers of that time with a number of methods which enabled them to study physiological processes quantitatively and to elucidate the chemical processes taking place in the organism. The graphic method of recording elaborated by Helmholtz, Ludwig, Marey and others made it possible to record with accuracy such processes as the contraction of muscles, the propagation of electrical changes in the nerves, the variations in pressure in the blood vessels, in the heart, etc. This enabled physiologists to measure changes occurring in physiological processes during short periods and to reveal phenomena which cannot be observed without objective registration. In this way, for example, the connection between the variations in blood pressure in the vessels and the phases of cardiac activity (Marey, Ludwig) were investigated and the rate of conduction of excitation in the nerves (Helmholtz) measured.

In the second half of the 19th century, due to the study of the cellular structure, it proved possible to find the link between the activity of various organs and the structural peculiarities of the cells and tissues of which they consist. Definite tissue structures with which the functions of the organism are connected were discovered (for example, the connection between the activity of the nervous system and the mutual disposition of the nerve cells and of their processes). The discovery of the law of conservation and transformation of energy made it possible to arrive at a quantitative description of physiological processes from the aspect of energy loss and energy accumulation (Meyer, Pflüger, Pashutin, Likhachov, Rubner).

In the second half of the 19th century, physiology attained great successes in describing the functions of individual organs and systems of the organism, as well as in studying some of the mechanisms regulating their activity. It may be said that by the beginning of the present century the significance of the functions of almost every organ was known in general outline at least. Physiology investigated the influence of the nervous system on the heart (Weber, Bezold, Cyon, Pavlov), on the blood vessels (Bernard, Ludwig, Walther, Ovsyannikov), on the skeletal muscles (Magendie, Helmholtz, Wedensky), on the smooth muscles of the alimentary tract and urinary bladder (Pflüger, Mislavsky, Langley). In the eighties and nineties, the physiology of digestion was investigated by Pavlov in such detail with new methods and from fundamentally new positions that to this day, essentially recreated by Pavlov, this is one of the most developed branches of science.

An important role in giving us our knowledge of the processes in the organism was played by the investigations of electrical phenomena in living tissues, mainly in the nerves and skeletal muscles, which were started at the close of the 18th century by Galvani, and greatly developed only in the period between the forties and the eighties of the last century (Du Bois-Reymond).

Hermann and Wedensky, basing themselves on a study of the electrical potentials arising as a result of stimulation of a nerve or muscle, created the concept of the so-called wave of excitation, or nerve impulse.

The second half of the 19th century witnessed the progress of research into the inborn (unconditioned) reflexes in all animals of a given species. The results of this research were of great importance, for they revealed the inborn mechanisms regulating the activity of various organs and enabled us to diagnose disorders of the nervous system (details can be found in Chapter 60). The discovery by Pflüger in the early fifties of the irradiation of excitation in the nervous centres and, particularly, the discovery by Sechenov in 1862 of the phenomena of inhibition in the central nervous system, gave rise to the study of the factors which determine the nature of inhibition and its role in reflex activity. Since then the study of the activity of the central nervous system invariably includes the phenomena of inhibition, because normally in the nervous system (and consequently in the entire organism) not a single phenomenon exhibits inhibition without excitation.

In the second half of the 19th century, extensive research was carried out into the properties of various parts of the central nervous system; this research proceeded from observations on the consequences of extirpation or stimulation (see Chapter 64) of different parts of the brain and spinal cord (Flourens, Magendie, Goltz, Fritsch and Hitzig, Ferrier, Mislavsky, Bekhterev and others).

The same period witnessed important investigations into the properties of the organs of vision and audition (Helmholtz) and the study of the role of nervous apparatuses (receptors) located in the internal organs and skeletal muscles and stimulated when their activity changes (Sechenov, Hering, Pavlov, Sherrington, Ludwig, Cyon).

The elaboration of problems relating to intermediary metabolism—transformation of glucose into glycogen (Bernard), transformation of products of protein metabolism in the liver (Nentsky, Pavlov), etc., was likewise begun in the second half of the 19th century. The study of the chemical composition of various organs and tissues in the animal body, as well as of the chemical processes of transformation taking place in it, has developed into a special chemical branch of physiology.

In briefly touching upon the development of physiology in Russia, we have to state that among the important achievements of science in the first half of the 19th century were the investigations carried out by Walther and Basov. In 1842, Walther (1817-1889), a pupil of N. Pirogov, showed that a cross-cut of the "sympathetic nerve threads admixed to the sciatic nerve of a frog" (i.e., of the sympathetic nerve fibres) caused a dilation of the vessels of the web. In the same year Basov (1812-1879) elaborated a method of penetrating the stomach of an absolutely healthy animal by applying a stomach fistula and, for the first time in the history of physiology, demonstrated the feasibility of a protracted, chronic experiment. However, Walther and Basov did not appreciate the importance of their discoveries and did not develop them. Claude Bernard was the man who elaborated the theory of innervation of blood vessels. But it was Pavlov who turned the method of investigating physiological processes in normal, healthy animals into an instrument which revolutionized the entire development of physiology.

The works of Sechenov marked a new stage in Russian physiology.

Sechenov was born in 1829 in the former Simbirsk Gubernia. In 1850, after a short period of service in the army as an officer in the engineering corps, he entered the medical faculty of Moscow University. There, under the guidance of Glebov and Orlovsky, he learned the principles of experimental and theoretical physiology. Not only the medical faculty, but the university as a whole, with its intense activity, together with Granovsky's lectures on history and the ideological atmosphere created by the philosophical works of the revolutionary-democrat A. Herzen, played an outstanding role in forming Sechenov's world outlook. His materialistic views, which underlay all his creative work, took shape already in his student days at the university.

In 1856, after his graduation, Sechenov went abroad on a scientific mission. There he worked in the laboratories of Ludwig, Helmholtz and Claude Bernard.

Upon his return to Russia, he headed the chair of physiology of the Medico-Surgical Academy (later renamed the Military Medical Academy) in Petersburg.

I. Sechenov

In 1862, Sechenov discovered the phenomenon of inhibition in the central nervous system, and in 1863, he published his brilliant work *Reflexes of the Brain*, in which he gave a consistently materialistic interpretation of mental phenomena. This book made him a political suspect in the eyes of the tsarist government, and only the fear of attracting still greater attention to this work compelled the government of Alexander II to give up the idea of taking legal action against Sechenov. Subsequently, Sechenov worked at the Odessa, Petersburg and Moscow universities. He died in Moscow on November 15, 1905.

Sechenov has gone down in the history of science as a great scientist and thinker; he was the first to subject the most intricate domain of nature—the phenomena of consciousness—to a natural-scientific analysis.

Sechenov had many pupils, some of whom became prominent scientists. For example, N. Spiro discovered the so-called reciprocal inhibition in antagonistic centres (the fame of the English researcher Sherrington is due to a large extent to his thorough elaboration of this problem). V. Pashutin (1845-1901), another of Sechenov's pupils, founded the Russian school of pathology (pathological physiology) and, jointly with A. Likhachov, was the first to work out precise methods of directly measuring the total heat produced in the human organism. The outstanding pharmacologist N. Kravkov was also a pupil of Sechenov, as was the prominent physiologist B. Verigo, who investigated the peculiarities of the action of a continuous current on the tissues and showed that the taking up and release of oxygen by haemoglobin play an important role in the carriage of carbon dioxide by the blood.

Sechenov's associates included M. Shaternikov (1870-1939), who studied general metabolism, and A. Samoilov (1867-1930), the prominent investigator of electrical phenomena in living tissues who first advanced the hypothesis of a chemical mechanism governing the transmission of excitation from the nerve to the skeletal muscle and from one neuron to another in the central nervous system.

Nikolai Yevgenyevich Wedensky (1852-1922) was one of Sechenov's pupils at Petersburg University; after Sechenov and Pavlov, he must with all justification be ranked among the leading Russian physiologists. In his remarkable experimental researches, Wedensky, who had participated in the revolutionary movement in his youth, advanced the important concept of the inner unity of the externally opposite phenomena of excitation and inhibition. A. Ukhtomsky (1876-1942) carried on Wedensky's researches and profoundly developed his ideas.

Among the physiologists who worked in Petersburg beginning with the sixties and seventies of the 19th century were I. Cyon who, together with K. Ludwig, proved the existence in the aortic arch of specialized sensitive formations—receptors stimulated by the rise of arterial blood pressure, F. Ovsyannikov (1827-1906) to whom science owes the study of the vasomotor centre and of a number of researches into the fine structure of the nervous system, and I. Tarkhanov (1846-1908), who is known for his discovery of the skin galvanic reflex.

A prominent place in the development of Russian physiology belongs to Kazan University, where N. Kovalevsky (1842-1891) and his successor, N. Mislavsky (1854-1929) used to work. Kovalevsky discovered that arterial blood pressure rises as a result of the accumulation of carbon dioxide in the organism. Mislavsky ascertained the exact location of the respiratory centre in the medulla oblongata and jointly with V. Bekhterev established that the stimulation of the cerebral cortex influences respiration and blood circulation.

Important physiological investigations relating to various branches of physiology were made by Professor V. Danilevsky of Kharkov (1852-1939), V. Chagovets of Kiev, and A. Kulyabko of Tomsk.*

But the most outstanding role in the development of physiological science as a whole was played by Pavlov.

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* Besides the above-mentioned researchers, a number of other Russian scientists (Babukhin, Bubnov, Sobolev, Rogovich, Betz, Sokovnin, Smirnov, Ustimovich, London and others) carried out important investigations, which are referred to in the corresponding chapters of this book.

Pavlov was born on September 27, 1849, in Ryazan. He received his secondary education at the local theological seminary. During his studies in Ryazan he read Pisarev, Chernyshevsky and Dobrolyubov. In 1870, he entered Petersburg University, graduating from the department of natural science in 1876, and later finishing the Military Medical Academy. In his student days, under the guidance of Cyon, he carried out his first research into the problem of innervating the pancreas. Beginning with 1878 he headed the research laboratory at the clinic of the eminent therapeutist S. Botkin in the Military Medical Academy. It was Botkin who, according to Pavlov's statement in the concluding part of his thesis, encouraged him to continue studying the influence of the nervous system on all physiological processes. Until 1890, Pavlov worked on problems of the physiology of blood circulation and, at the same time, started his investigations of the processes of digestion. From 1890 he headed the physiological department at the Institute of Experimental Medicine and the Chair of Pharmacology at the Military Medical Academy, where, in 1895, he was nominated professor of physiology. In 1907, after the death of Ovsyannikov, Pavlov was elected to the Academy of Sciences and became the head of its physiological laboratory (which in the Soviet period became an important physiological institute of the Academy of Sciences of the U.S.S.R., and now bears his name). During the last ten years of his life, Pavlov gave much of his attention to the biological station which, by decision of the Soviet Government, was organized for him in the village of Koltushi (now Pavlovo) near Leningrad. His numerous pupils worked under his guidance in various physiological laboratories, and the school he founded is not only the most advanced but also the largest.

In 1904, the highest international reward of that time—the Nobel prize—was conferred on Pavlov. Already at the end of the 19th century, after his *Lectures on the Work of the Principal Digestive Glands* had been published (1897), he became one of the renowned physiologists in the world; he was elected an honorary member of many academies, universities and medical societies.

At the turn of the century, having elaborated anew the physiology of digestion as a consistent theory of the development of digestive processes in the organism of a normal animal, Pavlov started his still more complicated research in the highly responsible sphere of natural science where no one had ever before dared to experiment. Proceeding from Sechenov's ideas, Pavlov created a real physiology of the brain.

In 1935, i.e., a year before his death, the International Physiological Congress held in Leningrad and Moscow under the chairmanship of Pavlov, conferred on him the title of *princeps physiologorum mundi.*

General Characteristics of the Physiology of the Pre-Pavlovian Period

The physiology of the pre-Pavlovian period was almost exclusively an analytical science, i.e., it studied only particular processes artificially isolated from the integral activity of the entire organism. The physiologists of the 19th century accumulated a multitude of facts relating to the functioning of separate organs, but were unable to show the interdependence of the various functions of the organism as a whole *in normal conditions of its existence.* This is indissolubly connected with the essence of the purely analytical method of knowledge and proceeds from the metaphysical concept of nature. The analytical method applied by the physiologists of the 19th century, who studied separate phenomena, in isolation from the integral whole, divorced the particular from the general, the simple from the complex. The elements thus isolated in the course of the analysis were *regarded as constant, independent and participating in the integral phenomena as separate entities*. The picture of an integral process or the properties of an integral structure were said to be the result of various combinations of "elementary" units which the researchers had been able to disclose by decomposing complex phenomena (for example, the properties of cells, individual reflexes, individual nervous impulses). From this point of view, the organism was regarded as a "cellular state" (R. Virchow), as a sum of cells whose properties were considered separately from the process of development and from the interaction of the organism with surrounding nature, as something pre-established, given beforehand. Pathological processes in the organism were regarded as a sum of the disturbances in the vital activity of individual cells. The reactions of the organism to the influences of the external environment were, in the main, considered as predetermined by the properties of corresponding organs and groups of cells (for example, the group of cells constituting each reflex arc) and not as elaborated in the course of the interaction between the organism and its environment.

As a result of the metaphysical approach to natural phenomena, physiologists often studied the functions of separate organs and cells without regard for their connection with the vital activity of the whole organism developing in definite conditions of the environment. Following Virchow, physiology prior to Pavlov supposed that the accumulated facts concerning the activity of various, individually investigated, organs and cells were sufficient to form a correct notion of the normal functions of the organism as a whole, and confined itself mainly to the method of acute experimentation and to the study of isolated organs, i.e., to methods which fully exclude any investigation of the *normal* influence of the nervous system on all physiological processes *in the natural conditions of existence*. Although a number of investigations (such as the study of total metabolism, heart rate, temperature of the body, etc.) had been carried out prior to Pavlov on integral, intact organisms, they were based not on new principles, but only on modified methods of research, and the appeal of certain researchers (for example, of Claude Bernard) to study the functions of the organism in its normal development found no embodiment in experimentation. The analytical physiology of the 19th century studied only those forms of the nervous activity which were inborn reflexes and which were regarded as invariable, permanent "units" of the activity of the nervous system, as processes which were studied almost separately from the activity of the higher nervous centres. The more or less constant influences exerted by the nervous system on the functions of various organs, which were revealed in the course of acute experiments (vivisection), were considered the only form of nervous activity accessible to natural-scientific investigation. Thus, all the higher forms of activity of the central nervous system determining the behaviour of the organism in the surrounding medium were excluded from the sphere of physiological research. This led to a dualistic division of all phenomena in the organism into two fundamentally different categories—phenomena of "internal," "vegetative" life covering all functions which by their significance are common to all animals and plants (metabolism, nutrition, respiration, etc.), and phenomena inherent only in animals—phenomena of "animal" life which determine the entire behaviour of animals.

However, it would be erroneous to underestimate the great importance of the facts obtained by analytical physiology. These facts underlie our knowledge of the functions performed by the greater part of the organs of the body, and they have provided highly important material for the development of medicine; compared with the state of science in the 18th century, they signified a considerable advance in the knowledge of the vital activity of the organism.

In accumulating facts, most physiologists of the 19th century held to positions of spontaneous materialism, which in the last century was characteristic of the development of natural science in general. But the spontaneous materialism of the 19th century was limited by its metaphysical concept of nature. Ignoring the possibility of the rise of qualitatively new forms of activity in living matter in the process of development and examining all phenomena without regard for their changes and interconnections, the metaphysical concept of nature could not explain such phenomena as the origin of life, the rise of sensations and of higher forms of nervous activity. Therefore, when expounding these problems, the naturalists of the last century either advanced primitive and mechanistic propositions which actually prevented any genuine study of the most complex vital phenomena (vulgarizers of materialism of the fifties-seventies—Vogt, Moleschott and others), or arrived at agnosticism, asserting that the origin of life, sensations and consciousness are fundamentally unknowable (DuBois-Reymond, Helmholtz, Claude Bernard). Thus, they actually paved the way for the spread of vitalism and of undisguised idealistic concepts in the theory of knowledge. In physiology, this trend was advocated with particular persistence by Johannes Müller (in the thirties and forties of the 19th century) and by his followers (Verworn, Hering, Uexküll and others).

Being a strictly analytical science which proceeds from the metaphysical concept of nature, the physiology of that time could not approach the knowledge of the normal activity of an integral organism and the study of the physiological processes determining the activity (behaviour) of the organism in the surrounding medium. A radical change in the whole attitude towards the study of the activity of animal organisms was necessary if new trails were to be blazed in physiology. This radical change was accomplished thanks to the scientific exploit of Pavlov, the greatest naturalist of our time.

The Principles of Pavlovian Physiology

Pavlov's teaching is a science of the course of vital processes in an integral organism during its various natural relations with the surrounding medium. Pavlov himself defined the result of his work as follows: "Yes, I am glad that together with Ivan Mikhailovich (Sechenov), I and my group of dear colleagues have won for the mighty realm of physiological research, the animal organism, complete and undivided, instead of a vague half. And this, indisputably, is our Russian contribution to world science and generally to human thought."*

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* I. Pavlov, *Complete Works*, Vol. I, p. 13.

These words show that Pavlov's entire activity was devoted to the creation of a new trend in physiology, described by him as *synthetic physiology, since it considers each physiological phenomenon as an integral whole* in diverse conditions of its development.

In 1901, Pavlov wrote: "Judging by what we already know, synthesis, as a new method widely applied to the entire organism, will render great help to future physiological research. . . . The task of analysis was to study in the best way possible a definite isolated part; this was its original purpose. It was aimed at establishing the relation of this particular part to all possible natural phenomena. . . . The aim of synthesis is to establish the significance of each organ from its true and vital aspect, to ascertain its place, as well as its corresponding nature."* Thus *the indissoluble combination of analysis and synthesis* is one of the fundamental principles underlying Pavlov's research.

The normal course of development of physiological phenomena in an integral organism cannot be investigated on animals mutilated as a result of dissection, which usually takes place in vivisectional experiments. Beginning with his very first investigations in the seventies of the last century, Pavlov elaborated a new method for the study of blood circulation, and especially digestion, in absolutely normal animals, in conditions of *chronic experiments*. He worked out methods of surgical operation which made the internal organs of the animal accessible to investigation without deranging the normal state of the organism.

Any phenomenon in an integral organism invariably depends on its interconnections with the environment. In the organism of higher animals all connections with the surrounding world, as well as the interconnections of all the functions of the organism itself, are accomplishable due to the activity of the nervous system. In the process of evolutionary development these connections become more and more complex. An increasing role in bringing these connections about is played by the anterior parts of the central nervous system, which steadily progress in their development; in higher vertebrates this is the cerebral cortex. From this it follows that a knowledge of the activity of an integral organism may be gained only by studying the uniting and regulating role of the central nervous system and by examining each physiological process in its dependence on the influence of the nervous system. That is why Pavlov strove to disclose the nervous mechanisms of the phenomena he investigated. Already in 1883, he stressed the significance of *nervism* by which he implied "a physiological trend striving to extend the influence of the nervous system to the largest possible number of the organism's activities."**

When Pavlov started his researches, a number of reflexes were already known and were regarded as invariable responses of the organism brought about by the transmission of excitation from the receptive mechanisms to the working organs through the central nervous system. However, prior to Pavlov, reflexes were studied almost exclusively under artificial conditions—in the course of vivisection. Pavlov studied the reflexes that govern the activity of the cardiovascular and digestive systems under conditions of natural stimulation of the receptors. He pointed out (in 1894) that there are receptors, i.e., peripheral endings of the centripetal nerves in all internal organs and that "these endings penetrate all organs and their tissues. It must be assumed that these endings are extremely diverse and specific, like the nerve endings of the sense organs, each adapted to its *peculiar stimulus of a mechanical, physical or chemical nature.*"*

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* *Ibid.*, pp. 573-74.

** *Ibid.*, p. 197.

Pavlov regarded each phenomenon in the organism as being dependent on the reflex activity of the nervous system. But the extension of this principle to an interpretation of all aspects of the organism's normal activity made it necessary to re-create the theory of reflexes, since prior to Pavlov, all researchers, except Sechenov, regarded reflexes as permanent, invariable, inborn reactions of the organism effected by the activity of the lower parts of the central nervous system. The organism, however, can exist in a continuously changing external environment only if it responds to such changes with reactions which ensure, according to Pavlov, an "equilibration" with these constantly changing conditions of existence. In higher vertebrates this "equilibration" in its higher form is achieved by the activity of the most organized and most reactive part of the central nervous system—the cerebral cortex. It is precisely the cerebral cortex which primarily determines the behaviour of the organism as a whole.

Therefore, a knowledge of all the phenomena in an intact organism in various natural conditions of its existence requires studying all the manifestations of the activity of the central nervous system, including its higher parts. The important materialistic proposition on the causal dependence of the behaviour of animals and human beings on past and present conditions of existence demanded the examination *of all forms of nervous activity as reflex activity*, as causally conditioned by stimuli acting upon the organism.

This proposition was first formulated by Sechenov. Developing Sechenov's ideas on the determining influence of the external environment on the activity of the organism, Pavlov reconstructed the entire theory of reflexes. He proved that the notion of reflex can and must be applied to an interpretation of all aspects of the activity of the central nervous system, including phenomena designated as mental activity. Rejecting the idealistic view of the impossibility of making the activity of the brain known, Pavlov started studying the most complex physiological processes in the higher part of the nervous system—in the cerebral cortex whose activity underlies all the acts and states which are said to be mental. In his experiments, Pavlov demonstrated the specific features of the reflexes which are brought about by the activity of the higher part of the brain, i.e., *conditioned reflexes*.

Conditioned reflexes are formed in the course of life by the coupling of temporary connections in the cerebral cortex (see p. 34) and ensure the highest equilibration of the organism with the constantly changing conditions of environment. The disclosure by Pavlov of the peculiarities of the formation of conditioned reflexes and of their specific features enabled science experimentally to investigate the normal activity of the higher part of the brain—the cerebral cortex.

The theory of conditioned reflexes—of the higher nervous activity—smashes the reactionary concept of the existence of a so-called spiritual activity, essentially unknowable and inaccessible to precise materialistic investigation.

The extension by Pavlov of his natural-scientific materialistic research to the higher forms of nervous activity was based on the *principle of deter-*

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* *Ibid.*, p. 527.

minism; this principle means that each phenomenon is originated by a definite cause, which under similar conditions must invariably evoke one and the same action. Pavlov wrote: "A truly active mind regards the strict natural-scientific interpretation of life in its absolute entirety only as recognition of the operation of the causality law, which is the principal condition of all existing things."*

*The conviction that all phenomena of life "in its absolute entirety" are subject to determination induced Pavlov to extend the notion of reflex, as a determined reaction, to the activity of the higher part of the brain. Pavlov's teaching on the higher nervous activity developed and gave science its first experimental proof of Sechenov's idea that "... all acts of conscious and unconscious life are reflexes by origin."**

Considering all the forms of activity of the nervous system as being strictly determined, Pavlov at the same time taught that all nervous phenomena are adjusted to a definite material substratum (*the principle of structure*). In particular, this means that every conditioned reflex, whose physiological mechanism is a formation of a temporary connection (p. 42), is always determined by the activity of certain structural formations of the higher parts of the central nervous system which enter into new functional relations.

By studying physiological processes in their normal course, Pavlov actually translated into reality the principles of dialectical materialism that nature should be regarded as an interconnected and integral whole.

He investigated the formation of new variable relations of the organism with the surrounding medium, the development of new nervous connections and the inhibition of a number of previously elaborated reflexes, and thereby studied the dynamics of the activity of the nervous system in its continuous movement and change.

Pavlov showed the qualitative peculiarity of the new nervous connections formed by the cerebral cortex in the course of life—the conversion of imperceptible changes into manifest ones. This conversion is particularly pronounced during the formation of a conditioned reflex, the latter taking shape (arising) after a series of combinations of the indifferent stimulus with the agent producing an unconditioned reflex.

Thus, Pavlov's research paved the way for understanding the qualitative peculiarities of the highest forms of nervous activity. The investigation of the higher nervous activity based on further elaboration of the reflex theory (Chapter 51) and the discovery by Pavlov of the objective laws of this activity are an important landmark in the development of modern advanced natural science.

With abundant experimental data on the two basic nervous processes which determine the activity of the central nervous system, namely, excitation and inhibition at his disposal, Pavlov examined these contrary processes in their unity, at the same time noting their struggle and the conversion of each into its opposite.

All these characteristic features of Pavlovian physiology give us grounds for asserting that Pavlov's teaching is an important natural-scientific concretization of a number of principles of dialectical materialism.

Sechenov, Pavlov's great predecessor, declared that an organism cannot exist without a surrounding medium and advanced a consistently materialistic interpretation of the activity of all organisms, including the human organism. As distinct from the Virchowian views, the teaching of Sechenov and Pavlov holds that the properties of organisms and of their cells took shape during *evolutionary development*, that they underwent and continue to undergo modifications in the course of the organism's interaction with the surrounding medium. Pavlov's theory of conditioned reflexes represents the highest stage in the development of the theory of interaction of animal organisms with surrounding nature. It disclosed the laws governing the formation of new reactions of the organism both to agents acting in the external environment and to stimuli arising within itself.

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* *Ibid.*, Vol. VI, p. 427.

** I. Sechenov, *Selected Works*, Vol. I, 1952, p. 124.

Establishing the dependence of all activities of the animal organism on the influence of surrounding nature, Pavlov's teaching comes close to the teaching of Michurin which refutes the views of Weismann and Morgan and maintains that the properties of each species form as a result of the interaction between the organism and surrounding nature.

Like the teaching of Michurin, whose motto is not to await favours from nature, Pavlov's teaching is indissolubly bound up with practice. Although pre-Pavlovian analytical physiology brought to light a number of very important facts without which medicine could not have developed, it proved to be quite helpless when it came to using the influence of the external environment of the organism.

Pavlov's teaching provides a foundation for the development of all medical sciences. In 1900, Pavlov wrote, "physiological synthesis concurs with medicine and identifies itself with it. . . ."*

CHAPTER 2

GENERAL CHARACTERISTICS OF PRINCIPAL VITAL PHENOMENA

The Concept of Metabolism

More than eighty years ago, Frederick Engels defined life as ". . . the mode of existence of protein bodies, the most essential element of which consists in continual metabolic interchange with the external world that surrounds them. . . ."** Engels also pointed out that "protein is the most unstable carbon compound known to us. It decomposes as soon as it loses the capacity of carrying out the functions peculiar to it, which we call life. . . ."*** Therefore, the mode of existence of protein bodies under which they perform functions called life implies a specific state of proteins characterized by their extremely high variability. This is the property which determines the ability of living proteins to undergo continuous changes; when metabolism ceases, the living protein perishes, decomposes.

So far we do not possess sufficient knowledge of the nature of the chemical and physicochemical processes constantly developing in living proteins. These processes probably consist in the formation of combinations of protein with electrolytes and various chemical groups, separation of these groups from the protein and constant transformation of the protein micelles.

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* I. Pavlov, *Complete Works*, Vol. I, p. 575.

** F. Engels, *Dialectics of Nature*, 1950, p. 244.

*** *Ibid.*, p. 243.

The liberation and consumption of energy in the organism. The disintegration of complex organic compounds into simpler substances which takes place in the organism and is accompanied by a liberation of energy is called *dissimilation*. The opposite processes leading to the formation of new complex compounds from simpler ones are known as *assimilation*. The processes of assimilation are connected with consumption of energy, since the substances formed in the course of assimilation possess a larger amount of chemical energy than those from which they have originated. Dissimilation, on the other hand is, in the main, connected with liberation of energy. *Life is possible only when there is a constant and indissoluble interconnection between the phenomena of dissimilation and assimilation.*

In animal organisms, the so-called free energy of chemical reactions is utilized in the carrying out of any work (in particular, for the formation of compounds containing more energy than the initial ones). Converted into work, i.e., consumed, this energy is released when substances with a larger amount of energy disintegrate into compounds with a lesser amount of energy.

Therefore, assimilation requires the presence of simultaneous dissimilative processes.

Metabolism which is inherent in protein bodies and represents the most characteristic vital process is bound up with all the chemical transformations in a living system. That is why separate "protein," "carbohydrate," "lipoid," or "fat" metabolism never takes place in living systems; all metabolic reactions are connected in a single, integral whole, in which individual links can sometimes replace one another.

Certain enzymes, which are protein bodies themselves, invariably participate in metabolic processes in organisms. Vital phenomena are inseparably linked with the activity of a great number of diverse enzymes (this question is dealt with in detail in the course of biochemistry).

The Significance of Oxidative Processes

The processes of oxidation of complex organic substances (proteins, fats and carbohydrates) to inorganic and simple organic compounds (water, carbon dioxide, urea) represent the main source of energy in animal tissues. The oxidative (*aerobic*) processes, however, are only the *final stage* of the dissimilative processes. *Anaerobic reactions*, i.e., reactions which are not accompanied by oxygen consumption but lead to the *decomposition* of complex compounds into simpler substances, also take place in all tissues (both animal and plant). A typical example is the reaction $C_6H_{12}O_6$ (glucose) $\rightarrow 2C_3H_6O_3$ (lactic acid) $+$ 170 small cal. per gr. of the lactic acid formed.

The energy released during exothermal anaerobic reactions is utilized in the processes of cellular activity. However, the tissues of animal organisms cannot exist *for a long time* at the expense of anaerobic reactions, since the amount of energy produced by reactions of *anaerobic disintegration* of some compound is always much smaller than the energy of its *complete oxidation*. This is accounted for by the fact that products resulting from anaerobic disintegration still possess a considerable amount of potential energy. Thus, for example, the heat of combustion of 1 gr. of glucose is equal to 3,770 small calories, and of 1 gr. of lactic acid—to 3,600 small calories. Consequently, the heat production of the anaerobic disintegration of 1 gr. of sugar is equal to 3,770-3,600, i.e., 170 small calories, which is 20 times less than the amount of heat liberated during the complete oxidation of sugar. Therefore, to cover the requirements of the tissues in energy solely at the expense of the energy of the processes of anaerobic disintegration, the breakdown of considerable quantities of initial substances is necessary. This leads to the accumulation of a large amount of *products of disintegration* (for example, lactic acid, ammonia and other substances). As a result, a considerable change in the cellular chemism takes place; the products of anaerobic metabolism finally damage, paralyze and kill the cells. Therefore, reactions of anaerobic disintegration are of importance only as a necessary *intermediary* link in the chemical dynamics of the cells. The possibility of *oxidative* transformations, i.e., the *presence of free oxygen* in the medium surrounding the cell, is an *indispensable condition for the existence of an animal organism*. The higher the organic structure of the tissue, the sooner it perishes in the absence of oxygen.

Irritability and Excitability. Excitation and Inhibition

Irritability, stimuli and the threshold of stimulation. Irritability is the inherent ability of all living organisms to respond to alterations in the environment with diverse changes in their states and activities. The agents provoking such changes in the state of living objects are called *stimuli*, and their influences, which produce one change or another in the living object, are called *stimulations*.

Any physical, chemical or physicochemical alteration in the environment may act as a stimulus on any living system; when all such alterations reach a definite degree of intensity, they cause changes in the living objects which are disclosed by respective methods of investigation and sometimes, as in the case of the contraction of the skeletal muscles, can be observed easily even without any special apparatus. The minimal intensity of the agent, sufficient to produce a stimulation, is called the *threshold of stimulation*. The lower the irritability of the living object, the greater must be the strength of the agent in order to produce a change in its state, and hence the *higher* the threshold of stimulation; conversely, the higher the irritability, the *lower* is the threshold of stimulation.

The level of the threshold of stimulation depends, above all, on the properties of the stimulated living organism, as well as on the nature of the stimuli acting upon it.

Every stimulus produces a change in metabolism, which is the most common response of a living organism to stimulation. Besides, under the action of a stimulus of a definite strength differentiated tissues also respond with specialized reactions characteristic of the given kind of tissue, i.e., of the structural and functional peculiarities acquired by it in the course of evolution. For example, a muscle reacts to stimulation with changes in metabolism which result in a peculiar response—contraction. The stimulation of the glandular tissues likewise produces a specialized response—secretion.

Excitation and excitability. The peculiar reaction of each tissue, which is determined by its morphological and functional differentiation and expressed in activities inherent exclusively in the given kind of tissue, is called *excitation*. The ability of a tissue to respond in a specialized way, when as a result of stimulation it reveals its own *specific activity*, is called *excitability*. In physiology, it is mainly muscular, glandular and nervous tissues that are considered excitable. A characteristic feature of nervous and muscular tissues is that when excitation arises in one point of a muscle or nerve fibre it can be conducted very rapidly to neighbouring points of the same fibre. In a nerve tissue, the excitation can be transmitted at a very high rate (within small fractions of a second) from one nerve unit (neuron, see p. 37) to another, as well as from a nerve fibre to the innervated effector apparatus (for example, muscular or glandular).

Since the nerve fibres come into contact with all tissues, nervous excitation can bring any tissue or organ into an active state, or provoke changes in their activity. In the nervous system excitation is transmitted to any of its parts and to the effectors of the organism; it connects and unites individual organs and systems of the organism into an integral whole.

It has already been mentioned that diverse agents of the external environment can produce excitation and that the strength of various stimuli necessary to start such excitation is different for different tissues. Special apparatuses with a particularly high excitability with regard to strictly definite agents have developed in animals in the course of evolution. For example, the sensitive cells of the olfactory apparatus are put into a state of excitation by concentrations of odorous gaseous substances, even if they are so small that they frequently cannot be determined by modern physics and chemistry.

Consequently, there are specially differentiated tissues in the organism which are sensitive to the action of a number of stimuli; these tissues are brought to a state of excitation by definite stimuli even of a minimum intensity. Such a high sensitivity to definite stimuli is the property of special nervous structures—*receptors* (p. 36).

Sound vibrations, for example, act upon a special auditory nervous apparatus, but do not exert any influence, say, on glandular cells. The interrelations of the excitable systems in the organisms are such that often stimuli of negligible physical intensity bring about the manifestation of a considerable physiological effect.

The process of inhibition. An increase in the strength or frequency of the acting stimuli intensifies the effect of excitation to a certain limit beyond which any further increase in the strength or frequency of the stimuli leads to a decline in the effect of excitation or to its complete disappearance. The activity peculiar to the given tissue (for example, contraction of the heart muscle, carriage of excitation in a certain tissue) weakens or disappears; however, the tissue is not in a state of rest, since the suppression of the effect of excitation has been called forth by a definite stimulation. Such an active state of the tissue, when in response to the action of a certain stimulus no external symptoms of excitation manifest themselves, or when the already existing excitation declines, is called *inhibition*. In various tissues inhibition depends both on the functional state of the tissues and on the nature and intensity of the stimulation (this subject is dealt with in detail in Chapter 61).

CHAPTER 3

REGULATION OF PHYSIOLOGICAL FUNCTIONS

The Concept of Regulation of Physiological Functions

An organism can exist only when it responds to environmental changes with respective adaptive reactions. For example, an organism could not exist if it did not react differently to food substances and to noxious agents, if oxygen or water deficiency in the surrounding medium did not evoke adaptive reactions by it, etc. Only because of its diverse reactions to changes in the surrounding medium, as well as within itself, "each animal organism, as part of nature, is a complex and integral system. whose internal forces so long as it exists, are equilibrated at every moment with the external forces of the surrounding medium. . . . Thus, life as a whole, from the simplest to the most complex organisms . . . is a long series of equilibrations with the external environment—equilibrations which reach the highest degree of complexity."* These countless equilibrations of the organism are manifested in the organism's diverse reactions to the influence of agents of the surrounding world.

Physiological processes ensuring the adaptation of the organism to its surrounding medium belong to the phenomena of regulation. These phenomena are based on the interconnection of all organs in the animal organism. Only when there is such interconnection in the organism, are external and internal agents able to give rise to coordinated reactions in a number of its organs (contraction of the muscles. changes in blood circulation and respiration, etc.). Chemical interconnection, which is due to the transmission of various chemical substances from one organ to another by the fluids of the body (i. e., in a humoral way), cannot lead to rapidly changing and differentiated reactions that would correspond to the great diversity of acting agents. Therefore, in animals it is the nervous system which develops and acquires decisive importance in regulating the functions of the organism; the nervous system is connected with receptors—special structures which receive stimulations from the external and internal environment.

Nervous regulation is such an important key to the understanding of all processes in the organism that its study should precede any studies of general physiology.

The Process of Nervous Excitation

The nervous system is composed of a multitude of various nerve cells which usually have one long process or axon. and several short processes or dendrites. The nerve cell, together with all of its processes is called a *neuron.* The axons of the nerve cells extending from the central nervous system (or to the central nervous system from the receptors) are nerve fibres which are usually enclosed in myelin sheaths and sheaths of Schwann. These fibres come together and form more or less thick trunks which are called nerves. A nerve is made up of a great number of diverse nerve fibres, each of which represents a process of a definite nerve cell.

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* I. Pavlov, *Complete Works*, Vol. III, Book 1, p. 124.

Stimulation gives rise to excitation in the nerve tissue; it is typical of this excitation that it spreads very rapidly along the entire neuron and acts upon the cells which the axon of the stimulated neuron leads to. Here are a few examples. A classical object for the investigation of nervous conduction is the so-called nerve-muscle preparation of a frog, i.e., a frog muscle cut out of the body together with the nerve. If the nerve is stimulated in a certain point by the application of a mechanical, thermal or electric stimulus, the muscle innervated by the fibres of the stimulated nerve will contract. The same can be easily demonstrated on a human being: if the nerve trunks situated close to the surface of the body are stimulated through the skin by shocks of an induction or constant current, the muscles innervated by these nerves begin to contract.

Let us take another example—the electrical stimulation of the vagus nerve in a dog or cat (among the fibres of this nerve there are some which terminate in the heart, and some which terminate in the stomach and intestinal walls). As a result of stimulation, the contractions of the heart slow down or cease; the intestinal wall which is made up of smooth muscles, intensifies its slow, vermiform movements; the stomach begins to secrete gastric juice.

As excitation spreads along the nerve fibre, the latter comes into a state of excitation along all its points, from the point where the stimulus was applied. The process of excitation developing in one part of the nerve fibre is transmitted to the neighbouring part.

Any organ may respond to the excitation of the innervating nerve fibres, i.e., fibres which end in its tissues, either with a transition from a state of rest to a state of activity, or with an intensification of the already existing activity and, in some cases, as is exhibited by the heart during the stimulation of the vagus nerve, also with a decline in this activity, i.e., with inhibition. However, the common feature is that the *activity or state of any organ changes if the nerve fibres which innervate it come into a state of excitation.* Consequently, nervous excitation is a process which changes the physiological state of the structures where the excited nerve fibres terminate. These are either the tissues of various organs of the body (for example, muscular, epithelial or connective tissue), or other nerve cells. In the latter case, excitation arising in one neuron produces excitation or some other change in another neuron. According to Pavlov, nervous excitation is a stimulatory process.

Nervous Impulses

The spreading process of nervous excitation is of an oscillatory, intermittent character. This has been established by the study of electrical phenomena arising in a nerve during its excitation. When a nerve fibre (or a nerve cell) undergoes excitation, its excited region becomes electronegative in relation to the regions which are still at rest; this is due to the appearance of an excess of negatively charged ions on the external surface of the nerve fibre, in the region which is affected by excitation. Therefore, by connecting an oscillograph—a device recording rapid and weak electrical oscillations—to two points of the nerve—one of which is affected by the process of excitation and the other is at rest—it is possible to record the difference of potentials between the excited and the resting region of the nerve fibres (Fig. 1).

Each region of the nerve becomes negatively charged when it is excited; this electronegativity grows, reaches its peak and then disappears within several thousandths of a second (in some nerve fibres of mammals this happens within a few ten thousandths of a second). After that, if the stimulation is continued, electronegativity develops anew, and disappears again just as rapidly. Thus, when a number of repeated stimuli, or even a continuously acting stimulus, is applied to the nerve, consecutive oscillations of the electrical potential are observed in each point of the nerve fibre. Any intensification, quickening or prolongation of the stimulations do not eliminate the intermittence of the action currents which are led off from the nerve and characterize the process of propagation of the oscillating, wavelike excitation of the neurons.

The negative electric potential of the excited part of the neuron can depend only on the physicochemical changes developing in the excited part as rapidly as electronegativity.

Consequently, a number of very rapid and easily convertible reactions take place in the nerve tissue during excitation; they condition the transitory accumulation of an excess of negatively charged ions on the surface of the excited part of the neuron.

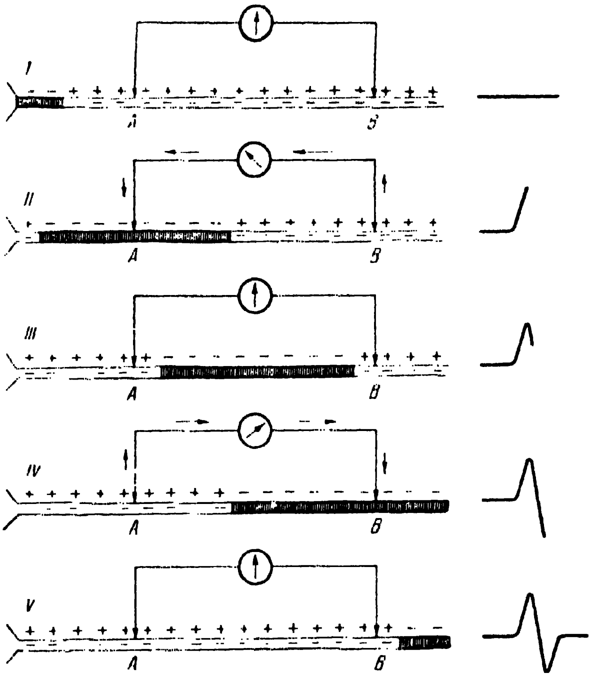

Fig. 1. Illustrating the emergence of action currents when a nerve impulse spreads over the nerve fibre.

The zone of the nerve fibre affected by excitation at the given moment is shaded. The signs + and show the distribution of positively and negatively charged ions inside the fibre and on its external surface. Sections "A" and "B" are connected with the oscillograph (the circle with arrow shows direction of the current).

I. Excitation running along nerve fibre from body of nerve cell has not yet reached "A". Therefore, between "A" and "B" there is no potential difference. *II.* Excitation has affected zone "A"; section "A" is electronegative in relation to "B": the mirror of the oscillograph is deflected, which is fixed in the record of the action current as an ascending bend (right side of the figure). *III.* Excitation, spreading along the nerve, has left section "A" but has not yet reached section "B"; the potential of these sections is, therefore, again equal, and the mirror of the oscillograph returns to zero position. *IV.* Excitation has reached section "B" which is now electronegative in relation to section "A". (The oscillograph, therefore, records the emergence of a current running in the opposite direction to that fixed in record *II.*) *V.* Excitation has left sections of nerve connected with oscillograph, and potential difference between sections "A" and "B" again disappears

The transitory, rapidly developing (within hundredths, thousandths and ten thousandths of a second) and as rapidly falling excitation, which spreads along the neuron and is characterized by a change in the physicochemical properties and electric potential of the part of the neuron excited at the given moment, is called a *nerve impulse*. Each nerve impulse is characterized, as it were, by a separate cycle of chemical and physicochemical changes propagated over the neuron and determining the rise of a potential difference between the part of the neuron which is in a state *of excitation at the given moment and those of its parts which are not yet excited (or are already emerging from the state of excitation).*

This potential difference is known as the action current, action potential, or bio-electrical current (these terms are also used to denominate the potential difference which arises during the excitation of other tissues).

The investigation of action currents is now a very important method of studying the phenomena that develop in the nervous system during the conduction of impulses of excitation; it makes possible the direct study of changes occurring in the nerve tissue at extremely short intervals — within thousandths of a second.

The Concept of Receptors

In normal conditions, excitation arises in the nervous system under the action of stimuli upon special nerve structures—receptors. The receptors are nervous, often nervous-epithelial, structures transforming the energy of external stimuli into a process of excitation which is conducted, in the shape of nerve impulses, to the central nervous system along nerve fibres extending from the receptors.

The receptors can come into a state of excitation if the intensity of the stimulus is very low, even when it is so low that, being applied directly to the nerve fibres, it does not excite them. For example, if a 1 : 10,000 concentration of quinine is directly applied to the sensory nerves, it does not produce any excitation, but the same concentration of quinine calls forth excitation when it acts on the taste receptors; this excitation produces impulses in the nerve fibres extending from the taste receptors, which are transmitted to the central nervous system.

A differentiation of the receptors takes place in the course of evolution: definite groups of receptors acquire the ability of transforming the action of definite stimuli, even of very insignificant intensity, into nervous excitation. Thus, receptors are structures which not only receive stimulations, but, so to speak, select them: in natural conditions each type of receptor reacts to a strictly definite kind of stimulus. Some receptors are effected by mechanical stimulation (*mechanoreceptors*), some by the action of heat or cold (*thermoreceptors*) and some by the action of chemical agents (*chemoreceptors*). There are also receptors which are excited by air (sound) or electromagnetic (light) waves. The morphological structure of the receptors is quite diverse; it varies from the free nerve endings to the highly complex structures of the eye and ear.

Receptors fall in two large groups:

1) *Exteroceptors* (external receptors) which are stimulated by agents of the external environment. They include:

a) receptors of the skin and of the mucous membranes of the mouth cavity, nasal cavity, upper respiratory tracts, cornea (tactile, thermal and pain receptors);
b) receptors receiving the action of special chemical substances, namely, taste and olfactory receptors;
c) auditory receptor;
d) visual receptor.

The latter two receptors (as well as the thermal and olfactory receptors) can be stimulated by agents which are situated at a distance from the organism and are, therefore, called "distant receptors."

2) *Interoceptors* (internal receptors) which are stimulated mainly by agents arising within the organism itself. They include:

a) *mechanoreceptors* stimulated by movements of the organ (skeletal muscles, heart, joints, etc.) in which they are located, as well as by changes in pressure within this organ *(baroreceptors)*:

b) *chemoreceptors* stimulated by various chemical agents which are formed in the organism (for example, carbon dioxide), or come into the organism from the external environment;

c) *thermoreceptors* stimulated by temperature fluctuations.

The interoceptors also include receptors of pain; they are stimulated by those agents which may harm the tissues.

Interoceptors are also distinguished according to the organs in which they are located. There are groups of receptors of various organs, such as vascular receptors, located in the walls of the blood vessels, tissue receptors (the latter implying chemoreceptors of any tissues stimulated by the products of tissue metabolism), receptors of muscles, tendons, joints and ligaments, i.e., receptors of the motor apparatus; the latter together with the receptors of the labyrinth (Chapter 69) are sometimes called proprioceptors, which is not a very felicitous term.

The difference between exteroceptors and interoceptors is in some cases not pronounced, since the receptors of the internal organs are sometimes stimulated by external agents (for example, when pressure is exerted on an organ through the skin, when hot or cold liquids get into the stomach, and air into the lungs).

Connection Between the Central Nervous System and the Receptors and Effectors

Nerve cells, whose axons connect the central nervous system with the receptors and thus form the so-called afferent nerve fibres, are called *afferent neurons*. Along these afferent or centripetal nerve fibres excitation is conducted from the receptors to the central nervous system.

Afferent nerve fibres are processes of cells located outside the central nervous system and concentrated mainly in the spinal ganglia of the cranial nerves. The spinal ganglia are situated in the cavity of the spinal canal, and the ganglia of the cranial nerves in the cavity of the cranium and in the openings of its bones.

Within a ganglion, the axon of the afferent neuron, at a distance of several microns from the body of the nerve cell which forms it, splits into two branches: one branch of the axon of each sensory neuron extends to a certain receptor, the other entering the spinal cord or medulla oblongata within the *posterior roots* of the spinal cord or the cranial nerves.

Internuncial neurons. In most cases, the afferent fibres entering the spinal cord or the medulla oblongata terminate at the cell bodies of the neurons whose axons do not extend beyond the central nervous system. These central neurons which are not connected directly by their axons with the receptors and effectors are called *internuncial* or *intermediary* neurons. The internuncial neurons are included in the pathway of excitation between the afferent and efferent neurons.

Each afferent fibre entering the spinal cord or the medulla oblongata has many ramifications and is, therefore, in contact not with one but with a series of neurons. Some of these internuncial neurons of the spinal cord and medulla oblongata project fibres which enter the cerebellum and the structures of the diencephalon (thalamus). From the nerve cells situated in these regions of the brain the excitatory process reaches the so-called subcortical centres of the strial region and the higher part of the central nervous system—the cortex of the cerebral hemispheres. This higher part of the nervous system, as we shall see later, acts on all the nervous structures of the lower parts of the central nervous system.

Excitation, coming from all receptors (except the olfactory and visual receptors) directly into the spinal cord and medulla oblongata and transmitted to new neurons, can always reach the cerebral cortex, the process of excitation invariably passing through a number of neurons.

The axons of definite cellular groups of the cerebral cortex descend to the lower divisions of the central nervous system. They conduct excitation in the opposite direction—from the cerebral cortex and the subcortical apparatus, often also through a number of internuncial neurons, to the terminal efferent neurons of the medulla oblongata and spinal cord, from which efferent nerve fibres extend to the working organs.

Thus, the process of excitation, which arises in the receptors and is conducted along the afferent nerve fibres to the spinal cord and medulla oblongata, can influence any elements of the central nervous system through a larger or smaller quantity of neurons, and from them act on the efferent neurons. The excitation (or inhibition) of the latter directly determines the accomplishment of reflex reactions of the organism to the stimulation of receptors.

The efferent neurons of the spinal cord and medulla oblongata are nerve cells whose axons connect the central nervous system with the various organs of the body and conduct to them the excitation which is caused in the nervous centres by the stimulation of the receptors. The nerve fibres transmitting excitation from the central nervous system to all the organs of the body are called *efferent*, or centrifugal nerve fibres; they emerge either from the spinal cord within its *anterior roots*, or from the medulla oblongata and midbrain within the cranial nerves. The organs which react to impulses transmitted to them along efferent nerve fibres are called *effectors* (for example, in winking, the muscles of the eyelids are the effectors).

Motoneurons. Efferent neurons whose axons conduct impulses that contract the skeletal muscles are called *motoneurons*. The cell bodies of the greater part of these neurons are located in the anterior horns of the gray matter of the spinal cord, while the axons of these nerve cells emerge from the spinal cord *within its anterior roots* and *are not interrupted anywhere* up to the fibres of the skeletal muscles.

Neurons of the vegetative system. All the efferent neurons besides those which transmit impulses that contract the skeletal muscles, i.e., *all the efferent neurons, except motoneurons, belong to the so-called vegetative nervous system.*

The term "vegetative nervous system" was introduced when the innervation of motor acts was erroneously set off as acts of "animal life," against the innervation of the internal organs with processes of "vegetative" life that allegedly had little to do with the external environment. There are no grounds for such a contraposition. The activity of the circulatory, ali-

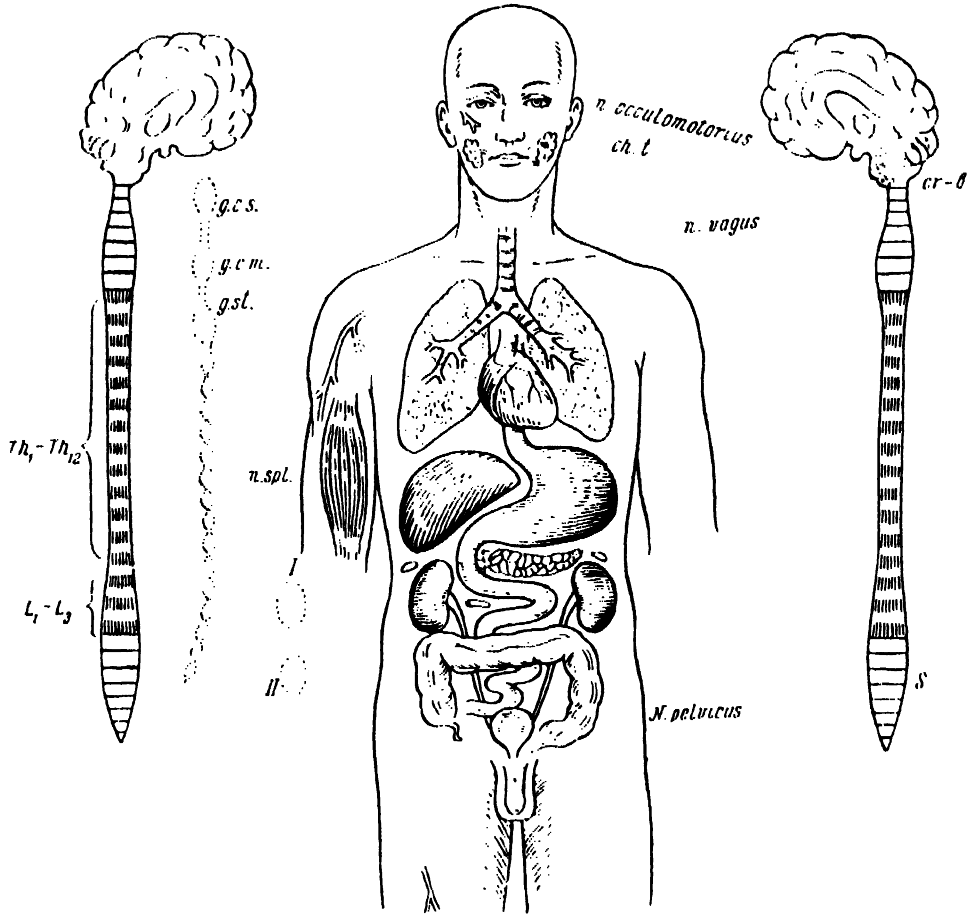

Fig. 2. Illustrating structure of sympathetic (left) and parasympathetic (right) divisions of vegetative nervous system.

Middle of figure shows to which organs sympathetic fibres (red lines) and parasympathetic fibres (blue lines) lead up. Solid lines designate preganglionic fibres, dotted lines show postganglionic fibres. Ganglia of sympathetic system are shown on left side of figure. Ganglionic cells of parasympathetic system, situated near or in the thick of the innervated organs, are shown in middle of figure as solid blue lines passing into dotted lines.

Left: *Th_1-Th_{12}* thoracic segments and *L_1-L_3* upper lumbar segments of spinal cord; *g.c.s.* superior cervical ganglion, *g.c.m.* inferior cervical ganglion, *g.st.* stellate sympathetic ganglion; *I* coeliac sympathetic ganglion and *II* mesenteric sympathetic ganglion; *n.spl.* splanchnic nerve (with a continuous fibre within it extending to adrenals).

Right: *cr.b.* cranio-bulbar, and *s.* sacral divisions of parasympathetic system; *ch.t.* chorda tympani.

mentary and excretory systems, as well as metabolism, are regulated by the central nervous system, as is the activity of the skeletal musculature. In both cases, this regulation is determined by influences coming from various receptors and consequently depends on all conditions of the external and internal environment. The excitation of the vegetative nervous system never arises in isolation and the efferent neurons constituting it only transmit the impulses arising in the central nervous system to the effectors. Therefore, the term "vegetative nervous system" (which was erroneously also called "autonomous" nervous system) should be understood only as a term which signifies groups of efferent neurons, whose location is characterized by definite peculiarities as compared with the motoneurons (Fig. 2).

The specific morphological feature of the vegetative nervous system lies in the fact that its nerve fibres issuing from the spinal cord or brain never directly reach the organs they innervate.* They invariably terminate at the nerve cells lying outside the central nervous system. These nerve cells form aggregations which are called ganglia of the vegetative system.

The nerve fibres of the vegetative nervous system which extend from the spinal cord, medulla oblongata or midbrain to the ganglia are called *preganglionic* nerve fibres. Excitation transmitted along them stimulates the nerve cells lying in the vegetative ganglia. Excitation arising in the ganglionic cells is conducted along the axons of these cells, which form *postganglionic* fibres, directly to the tissues of the internal organs. Thus, within the vegetative nervous system the excitation, spreading from the central nervous system to the effectors, passes through two neurons: a) one neuron whose cell body resides in the spinal cord, medulla oblongata or midbrain and whose axon forms a preganglionic fibre extending to the corresponding ganglion; b) the other neuron whose cell body lies in the ganglion and whose axon forms a postganglionic fibre which comes into contact with the cells of the innervated organ.

Two parts are distinguished within the vegetative nervous system: the sympathetic and the parasympathetic divisions.

1. The *parasympathetic division* is composed of: a) neurons whose bodies lie in the midbrain, medulla oblongata and sacral segments of the spinal cord and form preganglionic parasympathetic nerve fibres issuing from the central nervous system within the oculomotor, facial and vagus nerves, as well as the pelvic nerve; these fibres terminate at the neurons of the parasympathetic ganglia; b) neurons whose bodies lie in the parasympathetic ganglia and form postganglionic nerve fibres: the parasympathetic ganglia are always situated either in the very thick of the organs innervated by them, or in direct proximity of these organs.

2. The *sympathetic division* includes: a) neurons whose cell bodies lie in the lateral horns of the gray matter of all thoracic and upper lumbar segments of the spinal cord, and whose axons form nerve fibres issuing from the XII thoracic and III to IV upper lumbar segments of the spinal cord within its anterior roots; these fibres are preganglionic sympathetic fibres connected with neurons of the sympathetic ganglia; b) nerve cells of the sympathetic ganglia whose axons form postganglionic sympathetic fibres;

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* The sympathetic fibres of the vegetative system, which innervate the medullar tissue of the adrenals are the only exception. These fibres terminate directly at the cells of the medullar tissue of the adrenals.

the sympathetic ganglia are situated in the form of the so-called sympathetic chain in front of the vertebrae, and also lie in the abdominal cavity (the celiac and mesenteric ganglia).

The Concept of Reflex

The result of the action upon the central nervous system of impulses coming into it along afferent fibres from the receptors in each case depends on the kind of receptor subjected to stimulation, on the functional state of the central nervous system by the time the impulses begin to act on it, as well as on the strength and duration of the stimulation. The activity of the central nervous system, which is determined by impulses transmitted to it from the receptors, always influences the state of efferent neurons. If certain groups of efferent neurons are brought to a state of excitation under the influence of processes with which the central nervous system reacts to impulses coming from the receptors, the result is a transmission of the nerve impulses from the efferent nerve fibres to the organs of the body innervated by them. Reacting to impulses conducted to them along the efferent fibres, these organs pass from a state of relative rest to a state of activity or change their activity. Thus, the final response to the stimulation of a receptor is the emergence of certain activity, or a change in the current activity of the working organs.

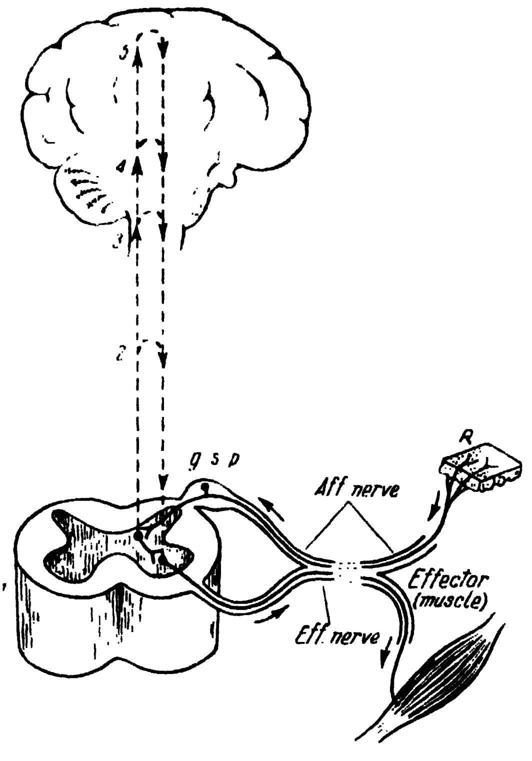

Fig. 3. Elementary scheme of unconditi efle

Nerve impulses arising during stimulation of are conducted along afferent fibres - "Aff. nerve"- (o: one fibre of this kind is shown) to spinal cord *(1)*, wh through internuncial neuron they are transferred to effer nerve fibres ("Eff. nerve"), and along latter reach effect Dotted lines show propagation of excitation from lov divisions of central nervous system to its higher divisic *(2, 3, 4)* including cerebral cortex *(5)*. Resulting char in state of higher divisions of brain, in its turn, acts (the arrows) upon efferent neuron and influences fi result of reflex act.

All the reactions of the organism determined by the response of the central nervous system to the stimulation of receptors are called reflexes. In other words, *reflexes* signify all the processes which develop in the organism in response to the stimulation of receptors, with the indispensable participation of the central nervous system. Among such reflexes are, for example, the following: winking as a reaction to the stimulation of the receptors of the cornea; contraction of the pupil under the action of light on the retina; swallowing as a result of the stimulation of the receptors in the soft palate by a lump of food; contraction of the urinary bladder in response to the distension of its walls; abrupt withdrawal of an extremity from the source of injurious (nociceptive) stimulation; secretion of saliva as a reaction to the stimulation of the taste receptors, etc. The excitation which is transmitted by the afferent fibres from the receptors to the nerve centres finds in those centres, as it were, a pre-established pathway, along which it proceeds to strictly definite efferent neurons and, consequently, to strictly definite working organs (to definite groups of muscles, glands, etc.). This gave rise to the concept of receptive fields of various reflexes and to the concept of the reflex arc.

The receptive field of a reflex. The receptive field of a reflex covers the receptors of that part of the body whose stimulation invariably evokes the given reflex. For example, the stimulation of the web and shank of a frog causes a characteristic reflex—the flexion of the leg; this area of the frog's skin is therefore called the receptive field of the flexor reflex. The area of the external surface of the thigh and back, whose stimulation brings the leg close to the back is called the receptive field of the rubbing reflex. The receptors of the cornea form the receptive field of the blinking reflex, etc.

The concept of the reflex arc. The reflex arc of any reflex is a *system of nerve structures the presence of which is indispensable for the accomplishment of the given reflex.*

The reflex arc of any reflex always includes: a) a receptor, b) an afferent neuron transmitting impulses from the receptor to the central nervous system, c) a nerve centre with an efferent neuron, and d) an efferent fibre extending to certain working organs (Fig. 3).

Here is an example. The stimulation of the receptors of the cornea reflexly makes the eyelids close. The reflex arc of this reflex is composed of: a) the receptors of the cornea, b) afferent neurons of the trigeminal nerve, c) neurons of the medulla oblongata along which the excitation is transferred from afferent fibres of the trigeminal nerve to the efferent neurons of the facial nerve, and d) efferent fibres of the facial nerve extending to the muscles of the eyelids.

If any link of the reflex arc is damaged, no reflex can be effected. For example, if the receptors of the cornea are paralyzed by cocainization, no excitation can be originated in them and transmitted to the afferent fibre; if the fibres of the trigeminal nerve extending from the receptors of the cornea are cut, the excitation originated in these receptors will not be able to reach the medulla oblongata; if a part of the medulla oblongata is damaged, the excitation coming from the receptors will, upon reaching the damaged centre, be unable to influence the efferent neuron; lastly, if the motor fibres extending within the facial nerve to the muscles of the eyelids are severed, the excitation transmitted in the medulla oblongata from the receptors of the cornea to the efferent neurons will not be able to reach the muscles.

The Concept of Conditioned and Unconditioned Reflexes

Prior to Pavlov, reflexes were considered only as reactions of the organism to the stimulation of receptors which, in the first place, always equally arise in animals of a definite species in response to the stimulation of the receptive field of the given reflex, and, in the second place, can be effected even in the absence of the higher parts of the central nervous system. Such reflexes were opposed to the so-called "voluntary movements" which depend on the activity of the higher parts of the brain. This led to the contraposition of the reflex regulation of the functions performed by the internal organs to the behaviour of animals in the surrounding medium, behaviour which was interpreted as voluntary action. Such a viewpoint doomed physiology to the renunciation of any research into the higher forms of nervous activity, i.e., into the activity of the cerebral cortex; it paved the way for agnosticism, and prevented the creation of synthetic physiology which deals with all phenomena in an integral organism normally functioning in surrounding nature. That is why the extension of the concept of reflexes, which led to the reconstruction of the entire theory of reflex activity, has blazed new trails in physiology.

Pavlov wrote that "as a system, the animal organism" exists in surrounding nature thanks only to the continuous equilibration of this system with the environment, i.e., thanks to definite reactions of the living system to stimuli reaching it from without, which in higher animals is effected mainly by means of the nervous system in the shape of reflexes."*

As mentioned above, the reflexes which had been known prior to Pavlov and designated by him as *unconditioned reflexes*, can be effected through the activity of the lower parts of the central nervous system. As a rule, they lead to reactions which are similar in all individuals of the given species: this includes winking in response to the stimulation of the cornea, coughing when foreign substances enter the larynx, as well as more complex reflexes not infrequently called instincts, for example, the alimentary, sexual and defensive reflexes. The nature of the organism's response in these reflexes depends on the character of the stimulus provoking them, i.e., on the kind of receptors on which it acts, as well as on its strength. In these reflexes there is always a *constant connection between the external agent and the responsive activity of the organism*, which, according to Pavlov, should be "rightfully called an unconditioned reflex."

"But the equilibrium attained by these reflexes," Pavlov pointed out, "is complete only when there is an absolute constancy of the environment. Since the latter, being highly varied, is always fluctuating, the unconditioned, or constant connections are not sufficient; they must be supplemented by conditioned reflexes, or temporary connections. For example, it is not sufficient for the animal to take the food placed before it—in this case it would often be hungry and die of starvation; the animal must discover the food by its various accidental and temporary symptoms, and the latter are precisely conditioned (signalling) stimuli exciting the animal's movement toward the food which ends with the introduction of this food into the mouth, i.e., in general, they evoke a conditioned alimentary reflex. The same is true of everything of importance for the well-being of the organism and the species, both in the positive and in the negative sense, i.e., for everything which the animal must take from the environment and against which it must be on its guard."**

Conditioned reflexes are new reflex acts which are formed during life; their formation is due to the establishment of temporary connections in the higher part of the central nervous system.

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* I. Pavlov, *Complete Works*, Vol. III, Book 2, p. 324.

** *Ibid.*

The following concrete examples will help to explain the mechanism governing the establishment of temporary connections. Not a single animal will exhibit any alimentary reaction (for example, lick its lips or rush to the place where it is usually given food) when it hears the sounds of a musical chord; nor will it manifest a defensive reaction when it sees an electric bulb blink. But the sounds of any chord can be easily converted into a stimulus producing an alimentary reaction: for this purpose it is necessary repeatedly to accompany it with the presentation of food. A defensive reflex to the blinking of a bulb can be as easily obtained if during this stimulation the animal is repeatedly subjected to the action of a noxious agent. If the sound of a whistle is regularly accompanied by the action of a pencil of rays on the eye, the pupil reflex (constriction of the pupil), owing to the formation of a conditioned reflex, will emerge at the sound of the whistle alone, which will be thus converted into a signal of the light stimulus.

If the action of any agent coincides in time with the action of a stimulus (usually of greater strength) which evokes an unconditioned reflex, there develops a conditioned reflex. After the formation of a conditioned reflex, the agent which has become a signal of the unconditioned stimulus evokes the same reflex reaction as observed in the unconditioned reflex. On the basis of each unconditioned reflex, it is possible to elaborate countless conditioned reflexes, if the agents, previously indifferent with regard to the given function, are accompanied by a stimulus evoking a corresponding unconditioned reflex.

Thus, *owing to the working out of conditioned reflexes any agent acting on the receptors can become a stimulus evoking any activity of the organism*. This makes possible the almost infinite multiplication and extension of connections between the organism and its surrounding medium. In the presence of unconditioned reflexes alone (which is the case with higher animals after the removal of the cerebral cortex), the animal will react neither to food nor to noxious agents even if the latter are at a close distance: in the first case, the animal will die from hunger in direct proximity of food, in the second, it will constantly be subjected to the action of the noxious agents. But the working out of conditioned reflexes ensures the organism's reaction to a multitude of agents which are *signals* of unconditioned stimuli. At the same time, unconditioned reflexes, after the working out of conditioned reflexes which are based on them, are usually effected not in a "pure" form: in natural conditions, the unconditioned stimuli always act in combination with a number of agents which become their signals. Therefore, normally reflex acts are complex reflex acts in which unconditioned and conditioned reflexes are indissolubly bound up.

Conditioned reflexes are constantly worked out not only as a result of the stimulation of the exteroceptors; they are also worked out when the interoceptors are stimulated (K. Bykov). The latter are stimulated with each change in the activity of the organs where they reside. For. example, in the course of muscular activity it is the mechanoreceptors and the chemoreceptors of the contracting muscles which are stimulated. When blood circulation and respiration are intensified, the interoceptors of the heart and of the large blood vessels of the lungs are stimulated simultaneously. Then impulses from the muscular receptors not only provoke definite unconditioned reflexes, but also play the role of signalling stimuli for the reflexes from the receptors of the large blood vessels and of the respiratory system. The reflex regulation of respiration and blood circulation appears here as a complex reflex act which combines the unconditioned reflexes from the receptors of the circulatory and respiratory systems, and the conditioned reflexes worked out (in this particular case) to the stimulation of the muscular interoceptors.

Thus, conditioned reflexes (and unconditioned reflexes) are included in highly diverse reflex acts. This leads to a very close interconnection of all the organism's reactions.

The conditioned reflexes represent the most perfect and the most dynamic form of interaction between the organism and the constantly changing conditions of the surrounding medium. They are caused by a great variety of agents whose action is reinforced by unconditioned reflexes, and become extinct due to the development of a process of inhibition, when the stimulus which has evoked the given conditioned reflex is no longer accompanied (reinforced) by the unconditioned stimulus.

The Analysers

Similar agents of the external environment, sometimes scarcely distinguishable from each other, such as various sounds, often serve as signals of the action of factors, which sharply differ in their biological significance. Some sounds, for instance, are produced by a beast of prey which may kill the given animal, others are food signals, etc. The animal can, therefore, exist only if it is provided with special mechanisms which ensure different reactions of the animal to different, often very similar, agents, or combinations of agents of the external (as well as internal) environment. These different reactions to different agents are possible thanks to that aspect of the activity of the higher nervous system which Pavlov called *analysing activity* (described in greater detail in Chapter 62) and which reaches the highest degree of development in the cerebral cortex. As a result of analysis, the great variety of stimuli acting upon the organism, as it were, breaks up into separate elements, and each change in the external or internal environment, separated by the analysing activity, may prove to be included in a temporary connection with only a definite reaction of the organism.

The analysing activity of the higher parts of the brain is based on the development of the process of inhibition (p. 34), and leads to definite conditioned reflexes being evoked by definite agents which are signals of the action of an unconditioned stimulus; similar agents whose action is not accompanied by a stimulation evoking the given unconditioned reflex, cause a process of inhibition in the cerebral cortex.

The analysing activity of the brain is indissolubly connected with its *synthesizing* activity, owing to which definite changes in the environment, separated by analysis, are unified in various complexes entering into a temporary connection with one activity of the organism or another.

The entire analysing (and synthesizing) activity is bound up with the functioning of definite structural formations of the nervous system. Combinations of nervous structures (receptors included) which ensure differentiated reactions of the organism to various stimuli were called ***analysers*** by Pavlov. The peripheral part of each analyser (visual, auditory, cutaneous, thermal, olfactory, motor, etc.) is represented by corresponding receptors. The particularly high sensitivity of each group of receptors to strictly definite changes perceived by the given kind of receptors, ensures by itself the most elementary and primitive analysis. The further stage of analysis can be effected by the lower parts of the central nervous system; it is owing to their activity that various stimulations of the receptors evoke different unconditioned reflexes. Therefore, each analyser, in the shape of its *conducting part* (Pavlov), includes (along with the peripheral part) the lower parts of the central nervous system. As to the higher analysis which ensures differentiated reactions of the organism to similar stimuli, its accomplishment is due exclusively to the analysing activity of the cerebral cortex. This activity is effected by the cortical part of the analysers.

Different analysers always function in combination with each other and ensure the elaboration of almost infinitely diverse reactions of the organism to various agents of the external and internal environment.

PART II

BLOOD AND LYMPH

CHAPTER 4

GENERAL CHARACTERISTICS OF THE BLOOD

Functions and Composition of the Blood

The blood is a fluid tissue that fills the blood vessels and ensures fluid (humoral) intercommunication of all organs by transporting various substances among them. Circulation provides the tissues with an uninterrupted supply of oxygen and nutritive materials transporting carbon dioxide and other metabolites from the tissues to the excretory organs—the lungs, the kidneys, the skin and the intestines. This transport role does not exhaust the physiological significance of the blood.

The blood together with the lymph and the interstitial fluid forms the *internal environment* of the body. The existence of the body and the normal activity of all its organs require a certain constancy in the composition and physicochemical properties of the blood which is maintained by regulatory mechanisms.

Certain specialized receptor structures and higher divisions of the central nervous system are particularly sensitive to changes in the composition of the blood and are involved in its fine regulation.

The next important function of the blood is protective. The white blood corpuscles take part in destroying the microbes which find their way into the body of the animal (phagocytosis). The blood plasma usually contains protein substances capable of agglutinating microorganisms, of causing their disintegration, as well as substances capable of rendering the toxins, i.e., poisons produced by the microorganisms, harmless.

The activity of various physiological systems is in some measure regulated through the blood. A number of physiologically highly active substances—hormones—enter the blood from the glands of internal secretion and are circulated by it throughout the body. Since the production of hormones and their passage into the blood are under the control of the central nervous system, the cerebral cortex in particular, the reactions involving the hormones are, in the final analysis, conditioned by reflex acts which are responsible for the interaction of the body with the external environment.

The blood, as a special tissue, appears in animals which have already reached a certain stage in their evolutionary development. Some of the lower multicellular animals, for example, sponges and Coelenterata, have no blood, and their tissues are in direct contact with the external aqueous environment which makes a direct metabolic exchange with the surrounding medium possible. In the echinoderms the gaseous exchange is also ensured by a flow of seawater through a water-transport system, but these animals also have cavities and vessels filled with an almost motionless fluid with colourless amoeboid cells. In some worms and molluscs the respiratory function is discharged by haemolymph, a fluid which contains certain dissolved respiratory pigments capable of transporting oxygen. Chromoproteins, i.e., complex proteins containing iron (haemoglobin, chlorocruorin and haemerythrin) or copper (haemocyanin), play the part of respiratory pigments. In the blood of the vertebrates the respiratory pigment (haemoglobin) is contained in special cells called erythrocytes or red blood corpuscles.

In vertebrates the blood is a fluid with suspended corpuscles. Its specific gravity varies between 1.050 and 1.060. If we add anticoagulants to the blood in order to prevent coagulation and let it settle, or, still better, centrifuge it, we can divide it into two layers. The lower layer consists of erythrocytes which settle to the bottom because of their high specific gravity. The erythrocytes are overlaid by a thin film of white blood corpuscles and thrombocytes. The upper layer consists of the fluid part of the blood, the so-called *blood plasma*.

In man the corpuscles constitute 42 to 45 per cent of the total amount of the blood; 58 to 55 per cent is plasma. In males the number of the corpuscles is, as a rule, greater than in females.

To determine the volume of erythrocytes a so-called haematocrit is made use of. Two tubes with a scale of 100 divisions on the wall of each form the essential part of the haematocrit. The blood to be tested is aspirated into the tubes, and the tubes are clamped into a special frame which is fastened horizontally to the axis of the centrifuge. The centrifuge is set in fast rotation (3,000 to 4,000 revolutions per minute) and the centrifugal force drives the erythrocytes, which are heavier than the plasma, to the distal end of the tube. The volume of the erythrocytes is read off on the scale of the tube 10 to 15 minutes after centrifuging.

Quantity of Blood in the Body

Methods used in estimating the quantity of the blood. The methods now used in estimating the quantity of the blood consist in injecting into the blood a very definite amount of some substance which slowly leaves the blood stream. By determining the concentration of the injected substance in the blood after it has been equally distributed throughout the latter it is easy to measure the quantity of the blood. If the injected substance, for example a dye, spreads only through the blood plasma the quantity of blood plasma in the body is estimated directly by this method. Since we know the proportion of the plasma and the blood corpuscles we can easily estimate the amount of blood.

In practice, in order to estimate the quantity of the blood, some colloid dye (for example, Congo red) indifferent to the body is most frequently injected into the blood. The big size of the dye particles prevents it from leaving the blood stream and from penetrating into the erythrocytes, and the dye, therefore, spreads only through the plasma. Five to ten minutes after the dye has equally spread throughout the blood plasma a certain amount of the blood is taken and the volume of plasma in it is determined; the amount of dye is estimated in the latter colorimetrically. Since the total amount of the injected dye is known it is easy to calculate the volume of the total plasma and the total blood circulating in the blood stream. The use of glucose for the same purpose yields less accurate results because glucose rapidly passes from the blood into the tissues. The quantity of the blood can also be estimated by the amount of carbon monoxide combining with haemoglobin. The most reliable methods for estimating the total quantity of blood are those based on the injection of artificial radioactive isotopes into the blood, for example, artificial radioactive phosphorus. A certain amount of blood is taken from the vein of the subject under examination and some phosphate containing radioactive phosphorus is added to this blood. Some time later, when the radioactive phosphorus has penetrated into the erythrocytes, the latter are separated from the plasma by centrifuging and reinjected into the blood stream. Of course, the rules of surgical asepsis are strictly observed all through these operations. In the blood stream the erythrocytes containing the radioactive phosphorus mix with the whole blood. The exchange of phosphorus between the erythrocytes and the surrounding plasma takes place slowly, and for this reason the entire radioactive phosphorus, which has penetrated into the erythrocytes, remains during the first minutes in them and, consequently, in the blood. By taking a sample of the blood several minutes later and by determining its radioactivity it is easy to calculate its total quantity.

The quantity of blood in man constitutes about 7 per cent of the body weight (with possible variations between 5 and 9 per cent). The injection of a fluid into the blood increases its total volume for a short time. Losses of fluid, especially considerable haemorrhages, reduce the total quantity of the blood. However, the changes in the total volume of blood are, as a rule, insignificant and very short-lived because of the processes which regulate the volume of the fluid in the blood stream.

When the amount of fluid in the vascular system increases the fluid passes from the blood into the tissues (especially into the cutaneous and muscular tissues) and is also excreted by the kidneys. Contrariwise, when the volume of the blood in the vascular system decreases fluid passes from the tissues into the blood. Owing to this the amount of the blood plasma in the vascular system is restored much faster after a haemorrhage than is the number of erythrocytes.

A decrease in the volume of the fluid in the vascular system, which leads to a sharp drop in the blood pressure, is much more dangerous than a decrease in the number of erythrocytes and in the concentration of the blood proteins. A slow haemorrhage (or one frequently recurring in small portions), even if it results in the loss of large amounts of blood, is less dangerous than a fast (even smaller) loss of blood. A gradual decrease in the number of erythrocytes to 1/4 of their normal number (i.e., the loss of 3/4 of all erythrocytes) does not in itself lead to death, but the loss of 1/3 to 1/2 of the amount of blood, if it has occurred rapidly (arterial haemorrhage), is fatal. An injection of a considerable amount of blood or plasma (or fluids which replace blood if no blood or plasma are on hand) into the blood stream after extensive haemorrhages may save the life because the re-establishment of the normal blood volume leads to a rise in the blood pressure and thus ensures blood supply to the brain, the heart and the other organs.

Physicochemical Properties of the Blood

The viscosity of the blood depends mainly on the number of erythrocytes it contains. To estimate the viscosity of the blood the latter is passed through a capillary tube. The greater the viscosity the less blood will pass through the capillaries per unit of time. The viscosity of water is taken as the unit of viscosity.

In the instrument, which measures viscosity (viscosimeter, Fig. 4) blood and water are passed through similar capillaries under the same pressure. Let us assume that while the blood reaches mark 1 the water reaches mark 5. This means that the viscosity of the blood is 5. In healthy people the viscosity of the blood is between 4 and 5.

The higher the viscosity of the blood the more erythrocytes the blood contains per unit of volume. Therefore, whenever the relative number of erythrocytes in the blood increases (for example, as a result of fluid passing from the blood stream into the tissues or because of increased new production of erythrocytes) the viscosity of the blood also increases. This is observed in persons who stay for some time in the mountains and in certain ailments (polycythaemia, shock after extensive burns, and poisoning with certain gases) when the viscosity of the blood may reach 8. In anaemia, when the number of erythrocytes in the blood decreases, it may drop below 4.

Osmotic blood pressure. Osmotic pressure is usually measured by indirect methods. The *cryoscopic* method, when the *depression*, or the lowering of the freezing point of the blood is estimated, is the most convenient and widespread. The depression of the human blood constitutes 0.56 to 0.58° C. A solution containing one gram-molecule per litre has a depression of 1.86° C (molecular depression). Thus, the total molecular concentration in the blood plasma and in the erythrocytes equals approximately 0.3 gram-molecule per litre. By using Clapeyron's equation [$P = cRT$ where P is osmotic pressure, the concentration, R—the gas constant (0.082 litre-atmosphere) and T is the absolute temperature], we can easily estimate that the osmotic pressure in the blood plasma at a body temperature of 37° C constitutes $0.3 \times 0.082 \times 310 = 7.6$ atmospheres.

In the lower marine animals (ganoid fish included) the value of the osmotic blood pressure is not maintained on a constant level and varies with the concentration of the salts in the surrounding sea water. The osmotic pressure of the blood changes with that of the sea water. Animals living near the coast in river estuaries, which carry fresh water, can endure wide variations in the salinity of the sea water that surrounds them because of the high and low tides: the concentration of salts may increase or decrease by scores of times. Nevertheless, the animals endure the changes occurring in the osmotic pressure of the surrounding medium and of their blood with no ill aftereffect.

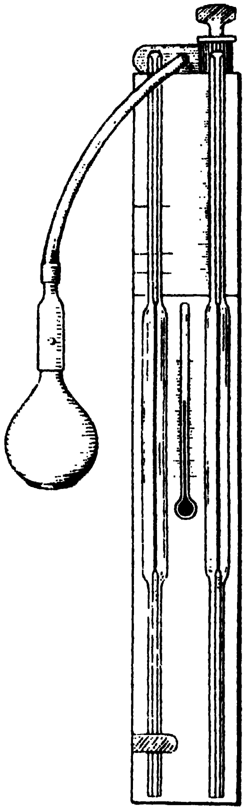


Fig. 4. Viscosimeter

In higher animals the changes in the osmotic blood pressure are negligible even when large quantities of water and salts pass into the blood. This is due to the fact that in the walls of the blood vessels there are special receptors (osmoreceptors) sensitive to deviations from normal osmotic pressure. The reflexes arising from the osmoreceptors aid in the passage of water from the tissues into the blood and back from the blood into the tissues, as well as in eliminating the water and salts with the urine. Owing to the retention of salts in the tissues isotonicity of the blood may be maintained for 2 to 3 days even in anuria, i.e., when the kidneys cease to excrete urine. The skin plays a particularly important part in regulating the content of water and salts. As the content of water in the blood increases the water passes into the connective tissue of the skin. Contrariwise, as the concentration of salts in the blood rises the water passes from the skin into the blood.

A distinct rise in the osmotic pressure of the blood occurs during very hard muscular work because of the production of low-molecular substances (lactic acid, carbon dioxide, etc.) from glycogen and other materials. A brief rest, however, suffices to re-establish the initial level of osmotic pressure.

The constancy of the osmotic pressure of the blood is especially important because the changes in the osmotic pressure of the tissue fluid in a certain measure correspond to the variations in the osmotic pressure of the blood. Sharp variations in the osmotic pressure of the tissues of vitally important organs (for example, the cerebral tissue) rapidly lead to disorders of the activity of these organs and even to their ruin. The constancy of the osmotic pressure of the blood is also important for the blood corpuscles, the erythrocytes, in particular. The osmotic pressure in the erythrocytes is the same as in the blood plasma. The membrane of the erythrocytes is permeable to water, sugar, urea and some other substances, and is impermeable to inorganic salts. Water passes through the cell membranes which have the properties of semipermeable membranes from a solution with a lower osmotic pressure into a solution with a higher osmotic pressure. The erythrocytes, therefore, swell up in hypotonic solutions (which have a lower osmotic pressure than the plasma) and shrink in *hypertonic* solutions (which have a higher osmotic pressure than the plasma). In *isotonic* solutions, i.e., in solutions whose osmotic pressure is the same as that of the plasma, the volume of erythrocytes does not change. When erythrocytes are placed in solutions with a much lower osmotic pressure than in the blood they may swell up to the point of bursting. In this case the content of the erythrocytes passes into the surrounding solution. This phenomenon is known as *haemolysis*.

Isotonic solutions must necessarily be used for safeguarding the erythrocytes when considerable amounts of liquid are injected into the blood for therapeutic purposes or when the blood is stored. A 0.9 per cent solution of sodium chloride is isotonic for man and is called a *saline solution*. If glucose, which is not an electrolyte and which has a much higher molecular weight (180), is used a 5.5 per cent solution will be isotonic.

CHAPTER 5

BLOOD PLASMA

Plasma Electrolytes

The total amount of mineral electrolytes in the blood plasma constitutes about 0.75 per cent.

The content of various ions (Table 1) is expressed in milligrams or 100 ml. of plasma (in mg. per cent) or milliequivalents per litre. If, for example, the blood plasma contains 20 mg. per cent potassium, i.e., 20 mg. per 100 ml., one litre of plasma will contain 200 mg. of potassium. The equivalent weight of potassium is 39 gr.; consequently, one milliequivalent corresponds to 39 mg., and the content of 200 mg. of potassium per litre of blood plasma may be expressed as 5.1 milliequivalents per litre.

The following table shows that the total amount of mineral cations exceeds that of the mineral anions. This indicates that part of the cations is connected with the anions of the organic acids. In addition to such organic acids as lactic acid, uric acid, etc., proteins also come into play as anions.

If we compare the total amount of cations and anions with that of all other constituents of the plasma (necessarily expressing all concentrations

Table 1

Electrolytic Composition of the Blood Plasma

Cations	Content		Anions	Content	
	in mg. %	in milliequivalents per litre		in mg. %	in milliequivalents per litre
$Na^{\cdot}$	300-330	130-144	Cl'	360-390	100-110
$K^{\cdot}$	16-20	4-5	HCO_3'	.	20-24
$Ca^{\cdot\cdot}$	8-12	4-6	H_2PO_4' & HPO_4'' for phosphorus	3.5	1-1½
$Mg^{\cdot\cdot}$	About 2	1	SO_4'' for sulphur	2-3	1-2
Total amount 140-155			Total amount		125-135

of the constituents in gram-molecules and in gram-ions) we shall find that the summary molecular concentration is determined primarily by the electrolytes. The content of sugar and of the intermediate products of protein metabolism, if we express it in gram-molecules, is not high. Proteins have an enormous molecular weight and despite their high content in the blood plasma by weight the number of gram-molecules is relatively small. The osmotic pressure of the blood plasma depends mainly on the amount of electrolytes in the blood, particularly on the quantity of sodium chloride whose content in the blood is subject to greater absolute variations than the content of the other electrolytes.

In experiments on isolated surviving organs a liquid containing salts, sugar, oxygen, etc., is perfused through their vessels. It has been found that in order to safeguard the vital activity of the isolated organs it is necessary to strive in addition to isotonicity also for iso-ionia between the tissue fluid and the perfused liquid, i.e., as much as possible for a similar ionic composition of the perfused liquid and the blood plasma.

The univalent $Na^{\cdot}$ and $K^{\cdot}$ cations turn out to be antagonists of the bivalent cation of calcium in a number of colloid chemical phenomena. Thus, for example, the univalent cations contribute to the swelling up of the colloids, while the $Ca^{\cdot\cdot}$ cation produces the reverse effect. The influence of univalent and bivalent ions on physiological processes is even more sharply pronounced. In certain concentrations the ions of potassium increase the excitability of the neuromuscular system, while the ions of calcium depress it.

If tissues are bathed in a solution whose mineral composition more or less appreciably differs from that of the blood plasma the activity of these tissues is soon paralyzed and the tissues die. Several liquids whose composition is very similar to that of the blood plasma have, therefore, been proposed for perfusion through isolated organs. The most commonly used are the fluids of Ringer, Ringer-Locke and Thyrode.

In addition to sodium chloride Ringer's fluid contains KCl, $CaCl_2$ and $NaHCO_3$ (Table 2). The presence of bicarbonate imparts to Ringer's fluid the character of a buffer solution (see below). Unlike Ringer's fluid that of Ringer-Locke contains glucose (0.1 per cent) and oxygen (the glucose serves to nourish the functioning organs). Thyrode's fluid also contains glucose and, additionally, salts of magnesium and of phosphoric acid which play an important part in the processes of intermediate metabolism.

Table 2

Salt Composition of Ringer's and Thyrode's Solutions

(in per cent)

Salts	Ringer's solution for poikilotherms	Ringer's solution for homoiotherms	Thyrode's solution
NaCl	0.6	0.8	0.8
KCl	0.01	0.042	0.02
$CaCl_2$	0.01	0.024	0.02
$NaHCO_3$ ...	0.01	0.01	0.01
$MgCl_2$......	—	—	0.01
NaH_2PO_4 ..	—	—	0.005

Concentration of H-ions in the Blood Plasma

Changes in the concentration of $H^{\cdot}$ and OH' ions in the blood plasma are of great importance.

The concentrations of hydrogen and hydroxyl ions expressed in gram-ions per litre are related to each other by a simple formula, namely, $[H^{\cdot}] \times [OH'] = K$, where $[H^{\cdot}]$ is the concentration of H-ions, $[OH']$ is the concentration of OH-ions, and K is the constant which at a temperature of 37° C equals 3.1×10^{-14}.

If we know the concentration of hydrogen ions we can easily calculate the concentration of the hydroxyl ions from this formula. Only the concentration of the hydrogen ions is, therefore, designated to characterize the acid-base balance. In view of the fact that the concentration of $H^{\cdot}$ usually equals only a very small fraction of a gram-ion per litre it is expressed in the form of a negative power of ten. In addition, the hydrogen index (pH), which is a negative logarithm of the concentration of hydrogen ions, is often made use of. In a neutral reaction and at 37° C $(H^{\cdot}) = (OH') = 1.77 \times 10^{-7} = 10^{-6.75}$. Consequently, the pH of a neutral solution at 37° C will equal 6.75, while the sum of pH and pOH for the same solution will be 13.50.

The pH of the blood plasma is about 7.36, i.e., the concentration of the hydrogen ions equals $10^{-7.36} = 0.000\,000\,043$ gram-ions per litre. The concentration of the OH-ions equals $10^{-6.14} = 0.000\,000\,72$ gram-ions per litre, i.e., it is about 17 times as high. The reaction of the blood is, thus, very slightly alkaline.

Buffer Systems

Under physiological conditions changes in the concentration of hydrogen ion in the blood are negligible, firstly, because of the presence of buffer systems in the blood and, secondly, because of the continuous physiological regulation of the acid-base balance effected by alterations in the composition of the buffer systems.

The buffer systems consist of a mixture of weak acids with the salts of these acids and of strong bases. The carbonate buffer system composed of carbonic acid and the bicarbonates of sodium and potassium is a typical example of a buffer system in the blood plasma.

Dissociation of carbonic acid as a weak acid is governed by the mass law:

$$H_2CO_3 \rightleftarrows H^{\cdot} + HCO_3'$$

$$[H^{\cdot}] \times [HCO_3'] = K \times [H_2CO_3]$$

$$\text{and, hence, } [H^{\cdot}] = K \times \frac{[H_2CO_3]}{[HCO_3']}.$$

Since the concentration of H_2CO_3 is directly proportional to the concentration of the dissolved carbon dioxide (CO_2) the last equation can be expressed as follows:

$$[H^{\cdot}] = K' \cdot \frac{[CO_2]}{[HCO_3']} \cdot$$

When both carbonic acid and bicarbonates are present the amount of anions formed during dissociation of carbonic acid is negligible compared with the amount of anions formed from the bicarbonates which dissociate almost completely. We may, therefore, without appreciable error consider the concentration of the HCO_3' ions equal to the concentration of the bicarbonates and replace the (HCO_3') in the equation by ($BHCO_3'$) where B stands for sodium and potassium. In this case we get an equation connecting the concentration of hydrogen ions with the formula of carbon dioxide and bicarbonate concentration:

$$[H^{\cdot}] = K' \frac{[CO_2]}{[BHCO_3']} \cdot$$

The K' constant equals $10^{-6.1}$. Thus, with a $10^{-7.36}$ hydrogen ion concentration in the blood plasma the amount of free carbonic acid in the form of carbon dioxide is approximately 1/20 of the amount of bicarbonates.

In addition to the carbonate buffer system the blood plasma also has a phosphate system (NaH_2PO_4, which yields the H_2PO_4' ion, and the Na_2HPO_4, which yields the HPO_4'' ion) and a protein buffer system. Haemoglobin, of which the blood contains a great deal, is the strongest buffer system in the blood (p. 64).

The carbonate buffer system possesses special properties because, on the one hand, the carbon dioxide can be quickly eliminated from the blood and, on the other hand, can be retained in the blood when the ventilation of the lungs is altered.

If some acid, for example, lactic acid from the working muscles, enters the blood it is neutralized by the bicarbonates and the amount of free carbon dioxide increases.

$$CH_3 \times CHOH \times COOH + HCO_3' + CH_3CHOHCOO' + H_2CO_3 \ .$$

Carbonic acid is an unstable compound and the greater part of it breaks up into CO_2 and H_2O.

Nevertheless, when the amount of free carbonic acid increases and the quantity of bicarbonates decreases the concentration of hydrogen ions in the blood rises. This is accompanied by an increased excitation of the respiratory centre. Owing to the increased ventilation of the lungs the carbon dioxide is eliminated from the blood into the expired air. Under these circumstances its content in the blood may fall not only to the original value, but even much lower so that the ratio (CO_2): (HCO_3') becomes the same as it was before lactic acid entered the blood despite the decrease in the amount of bicarbonates.

Thus, the physicochemical peculiarities of the carbonate buffer ensure the possibility for physiological regulation of the blood reaction by involving the respiratory apparatus (see Chapter 22). The above-cited formula $(H^{\cdot}) = K \times (H_2CO_3):(HCO_3')$ shows that the same reaction of the blood may be attained with different amounts of bicarbonate. The latter plays the part of a base reserve which is able to neutralize the acids entering the blood.

The carbonate buffer system enters into exchange reactions with the other buffer systems. The amount of bicarbonates in the plasma, therefore, depends on the amount of free carbonic acid and on the content of the other buffer systems.

The more free H_2CO_3, the farther the balance in the reversible reaction will shift to the right and the more carbonates there will be:

$$H_2CO_3 + HPO_4'' \rightleftarrows HCO_3' + H_2PO_4'.$$

The coefficient of carbon dioxide absorption for the blood plasma at 38° C is 0.510. This means that at a carbon dioxide pressure of 760 mm. Hg one ml. of plasma will dissolve 0.510 $cm.^3$ of carbon dioxide. According to Henry's law the amount of dissolved carbon dioxide is proportional to its partial pressure.

The content of bicarbonates in the blood and in the plasma is expressed in cubic centimetres of carbon dioxide which can be liberated from the bicarbonates by an addition of acid. Since the amount of the bicarbonates in the plasma depends on the amount of free carbonic acid (see above) the former is estimated under conditions of equilibrium with a gas mixture in which the partial pressure of carbon dioxide is 40 mm. Hg.

Since the bicarbonates are able to neutralize acids they are regarded as an *alkaline reserve*. The amount of bicarbonates per 100 ml. of blood plasma which is in a state of equilibrium with a gas mixture in which the partial pressure of carbon dioxide is 40 mm. Hg is referred to as the alkaline reserve or reserve alkalinity of the blood. In addition, the amount of bicarbonates is expressed in cubic centimetres of CO_2 (at 0° C and 760 mm. Hg) per 100 ml. of plasma.

Under certain conditions, particularly during hard muscular work, when large quantities of lactic acid are liberated into the blood, as well as in some diseases, in which big amounts of organic acids enter the blood (for example, in diabetes mellitus), the regulatory mechanisms which maintain the constancy of the H-ion concentration prove inadequate and the reaction of the blood shifts towards acidity. This condition is known as *acidosis*. During hard muscular work the shift in the reaction may express itself in a 0.1 to 0.2 pH decrease. A pH shift of more than 0.3 to 0.4 endangers life. When negligible amounts of acids enter the blood the changes in the composition of the latter may be confined only to a decrease in the alkaline reserve without reducing the pH of the blood. In these cases we speak of a *compensated acidosis*.

During increased elimination of carbon dioxide, for example, during hyperventilation of the lungs, there is a change in the reaction of the blood plasma towards alkalinity. This condition is referred to as *alkalosis*.

Blood Plasma Proteins and Their Physiological Function

The total amount of proteins in the plasma is 7 to 8 per cent. The proteins of the plasma may be divided into two fractions differing as to their physicochemical properties: *serum albumins* and *serum globulins*.

The serum albumins are proteins with nearly spherical particles and a molecular weight of 68,000. These proteins are water soluble and do not precipitate even when all the electrolytes are removed from the solution by dialysis or electrodialysis. When electrolytes are added the albumins are salted out with difficulty. The albumins do not precipitate when semisaturated with ammonium sulphate or when fully saturated with sodium chloride and magnesium sulphate; the serum albumins precipitate when fully saturated with ammonium sulphate. The human blood plasma contains 4 to 5 per cent albumins.

The serum globulins represent a group of proteins with a lower degree of dispersiveness and an unequal molecular weight, which is higher than 100,000. The molecules are more or less oblong. The globulins are insoluble in absolutely pure water and, therefore, precipitate on dialysis. In simple dialysis, however, a negligible quantity of electrolytes remains which proves sufficient for part of the globulins (the so-called pseudoglobulins) to be retained in the solution. In electrodialysis, when it is possible fully to remove the electrolytes, the pseudoglobulins also precipitate. The globulins are salted out when semisaturated with ammonium sulphate and when fully saturated with magnesium sulphate. Sodium chloride in full saturation only partly precipitates the globulins. The human blood plasma contains about 2.5 per cent globulins.

Recent investigations have shown that each fraction of serum proteins contains a considerable number (more than 30 in both fractions) of various proteins differing from each other in their physicochemical properties and physiological functions.

The total content of proteins in the plasma determines the colloid-osmotic or *oncotic* pressure of the plasma.

Of the total osmotic pressure of 7.6 atmospheres only 25 to 30 mm. Hg, i.e., about 1/30 of an atmosphere, is due to the presence of colloids in the plasma. This negligible pressure is due to the fact that there are relatively few protein particles, compared with the total number of molecules of the substances dissolved in the plasma, in view of the high molecular weight of the proteins. Nevertheless, this part of the total osmotic pressure is of essential importance for dividing the water between the blood and the tissue fluid (Chapter 8).

Inasmuch as the proteins of the plasma possess both acid and base properties they are capable of acting as buffers when acids and bases enter the blood. The albumins retain certain lipoids in solution and thus aid in their transport by the blood.

It was recently ascertained that the blood plasma proteins were directly involved in the protein metabolism of the whole body. The experiments in which amino acids with nitrogen tracer atoms (heavy isotope with an atomic weight of 15) were introduced into the body have revealed that the composition of the plasma proteins is renewed faster than that of the proteins of other tissues. It follows that the proteins of the plasma are intensively formed and, apparently, as rapidly consumed. It appears that the nitrogen balance of the body can be maintained by injections of plasma without consumption of food. This method is now used in feeding the sick who in certain diseases or because of a certain operation cannot be fed by mouth.

In addition to certain other factors (p. 68) the proteins of the blood plasma play an essential protective part when the body is attacked by infection. The immunity of the organism to infectious diseases, especially acquired as a result of an ailment or of inoculations, is, in a number of cases, due to the formation of protective or immune bodies of a protein nature which enter the blood plasma. Whenever some foreign protein (*antigen*) finds its way into an animal organism parenterally (avoiding the digestive tract) so-called *antibodies*, also of a protein nature, are formed in the organism. They are formed in the reticuloendothelial and lymphoid tissues. In some cases these substances render the poisons (*toxins*), produced by the microorganisms, harmless. These protective substances of the plasma or of the serum are called *antitoxins*. In other cases the substances formed in the blood serum either agglutinate the microbes (*agglutinins*), dissolve them (*lysins*), or precipitate the proteins foreign to the body (*precipitins*). The work of Soviet immunologists has demonstrated the great importance of the central nervous system *in the development of immunity, in the production of protective proteins and in their passage into the plasma.*

Coagulation of the Blood

Fibrinogen, one of the globulins of blood plasma, is usually considered apart from the given group of proteins because it possesses the remarkable property of becoming insoluble under certain conditions and assuming a fibrous structure thus changing into fibrin. The blood plasma contains only 0.3 per cent fibrinogen, but it is precisely its change to fibrin that is responsible for the coagulation of the blood owing to which the fluid blood turns into a dense clot within a few minutes.

Subsequently the clot gradually shrinks retaining the blood corpuscles and squeezing out the blood serum. In its composition the serum differs from the plasma only in the absence of fibrinogen.

Coagulation of the blood which occurs in every extravasation represents a complex and in some respects an insufficiently clear fermentative process (A. Schmidt). Fibrinogen changes to fibrin under the action of *thrombase* or *thrombin*. In the circulating blood this enzyme is found in an inactive state in the form of *prothrombin*. To change to thrombin, the active enzyme, prothrombin must be acted upon by *thrombocinase*, an activator, in the presence of calcium ions.

There is no thrombocinase in the fluid part of the blood; it resides in the tissues and in the blood corpuscles, namely, in the thrombocytes and in the leucocytes. The nature of thrombocinase is not yet sufficiently clear, but there are reasons to regard it as a complex of thromboplastic substances. The latter, apparently, include certain lipoids and, especially, certain lipoproteins, i.e., complex proteins which in addition to the protein part also contain lipoid groups.

To become active prothrombin requires the presence of calcium ions. Thus, coagulation of the blood or of the blood plasma requires four constituents: fibrinogen, prothrombin, calcium salts and thrombocinase. The blood plasma has only three of these constituents. Whatever the injury to the vessels with resultant extravasation the adjoining tissues are damaged and part of the blood corpuscles is destroyed. The blood is coagulated under the action of the thrombocinase liberated from the thrombocytes and the ruined cell bodies.

In addition to the aforesaid factors there is another protein of globulin nature which aids in accelerating the coagulation of the blood. Because of the absence of this protein the coagulation of the blood is retarded which, in its turn, is responsible for the bleeding in *haemophilia*.

In certain special cases the coagulated blood becomes liquefied again, as, for example, in the corpses of people killed in accidents. This is connected with the appearance of a special enzyme in the blood which is responsible for fibrinolysis, i.e., splitting the fibrin. Such blood is fit for transfusion to the sick.

This enzyme, apparently, enters the blood from the lungs at the moment of death. Pavlov was the first to discover a retarded coagulation of the blood as it flowed through the lungs during one of his experiments on a cardiopulmonary preparation. The passage of this enzyme from the lungs into the blood in accidents is dependent on influences exerted by the central nervous system (V. Ilyin).

Anticoagulants. The foregoing scheme of blood coagulation offers an idea *for preventing the blood from coagulating. The first method is to collect the blood with minimal injury* to the tissue and avoiding as much as possible any contact of the blood with the injured cells. However, the contact of the blood with the walls of a glass beaker is enough to start destruction of the leucocytes and thrombocytes, especially the latter. To prevent the coagulation of the blood for some time it is necessary to cover the walls of the beaker with a layer of liquid paraffin. But even this does not prevent the coagulation of the blood, but only retards it.

If shed blood is stirred by glass rods, glass beads, etc., the fibrinogen is deposited on the surface of these objects in the form of fibrin and the latter can be removed from the blood. After the removal of fibrinogen the blood no longer has any protein capable of producing a dense fibrous structure which forms the frame of the clot. Naturally, such defibrinated blood cannot coagulate any more.

Defibrinated blood is frequently used for studying the various properties of the blood. After separating the fluid part from the blood corpuscles we no longer have blood plasma. but serum. Defibrinated blood should not be transfused into an organism to make up for haemorrhages because it may have retained small clots which are likely to block fine blood vessels.

The best way to prevent the blood from coagulating is to remove or bind the calcium ions. Calcium can be precipitated by oxalates (2 mg. of $Na_2C_2O_4$ per ml. of blood) and by sodium fluoride or bound by citrates. However, the blood containing the least amount of oxalates (oxalated blood) or fluorine salts cannot be used for transfusion because these compounds are poisonous. On the other hand, blood to which sodium citrate was added to prevent coagulation (citrated blood) is widely used for transfusion. At a low temperature this blood can be preserved for 20 to 30 days and even longer (blood preservation).

Blood preservation has made it possible to save lives by transfusion after haemorrhages.

A big contribution to the development of the problem of blood transfusion was made by Russian scientists (V. Shamov, N. Yelansky et al.). Numerous transfusions were made during the Great Patriotic War; they helped to save the lives of many wounded combatants. Blood transfusions are also resorted to after serious operations.

There are substances which prevent the blood from coagulating by acting in a certain manner on the fermentative system. These include *hirudin*, extracted from the head of the leech, *heparin,* extracted from the liver and lungs of animals, and, finally, a number of synthetic dyes. The latest studies show that heparin is contained in the so-called "mast cells" located along the blood vessels. This warrants the assumption that heparin possesses the specific function of antithrombin, i.e., it prevents the blood from coagulating in the blood vessels when negligible amounts of thrombocinase are formed from disintegrating thrombocytes.

Variations in coagulation time. The coagulation of blood is of enormous biological importance since it prevents long-continued bleeding when a blood vessel is injured. In a special disease, called *haemophilia,* coagulation of the blood is greatly retarded for lack of one of the globulin proteins.

Haemophiliacs can easily die from extensive haemorrhages caused by even slight injuries.

Coagulation of the blood is also retarded in other diseases, for example, in vitamine K deficiency and in conditions interfering with the flow of bile into the intestines (obstructive jaundice) when vitamine K fails to be absorbed (p. 328). In such cases any surgical operation, especially on the parenchymatous organs, holds out the danger of profuse bleeding.

Preparations from coagulated ox plasma or fibrin films are used to stop bleeding. These preparations contain ready thrombin while the threads of fibrin applied directly to the bleeding surface serve as "embryonic" centres around which the blood fibrinogen of the operated person immediately begins to coagulate. Owing to this the entire bleeding surface is rapidly covered with clots.

Intermediate Products of Metabolism in the Blood Plasma

The blood always contains substances needed by the cells for their vital activity and the end products of metabolism which must be eliminated from the body.

If we precipitate all the proteins in the blood the filtrate will retain a number of nitrogenous substances: amino acids, urea, uric acid, creatinine and very small amounts of some other nitrogenous substances. The nitrogen of all these substances is called *residual* or *nonprotein* nitrogen. The blood of healthy people contains from 20 to 40 mg. per cent of it, i.e., 20 to 40 mg. per 100 ml. of blood. Most of these substances are almost equally distributed between the blood plasma and the erythrocytes. In certain renal diseases the elimination of nitrogenous metabolites from the blood, urea in particular, is deranged. The content of residual nitrogen increases and *azotaemia* results. Azotaemia is one of the symptoms of a pathological condition in which the products of metabolism normally voided with the urine accumulate in the body (*uraemia*).

The blood always contains sugar (glucose) and lactic acid as intermediate products of carbohydrate metabolism. Carbohydrates are absorbed in the intestines in the form of glucose; from the blood glucose passes into different organs where it is utilized as energy-producing material or replenishes the glycogen reserve in the cells. Under normal conditions the blood of man and of the higher animals contains 0.07 to 0.1 per cent (70 to 100 mg. per cent) on an empty stomach. After a meal rich in carbohydrates, especially sugar, the concentration of sugar in the blood increases, and *alimentary hyperglycaemia* is observed.

Lactic acid is an intermediate product of carbohydrate metabolism. During muscular rest the blood contains but little lactic acid, about 10 to 15 mg. per cent. During hard muscular work the amount of lactic acid in the blood may increase severalfold because large quantities of lactic acid are liberated into the blood by the muscles.

The blood plasma contains about 0.5 per cent fats, which is part neutral, part phosphatides (lecithin) and part cholesterol and its esters. After consumption of large quantities of fat, and in certain diseases (for example, diabetes), the content of fat in the blood plasma may markedly increase. This condition is called *lipaemia*.

CHAPTER 6

THE BLOOD CORPUSCLES

Form and Composition of Erythrocytes

In the lower vertebrates (fish, Amphibia, reptiles and birds) the erythrocytes are nucleated oval- or lentil-shaped cells. Under normal conditions the erythrocytes in man and mammals contain no nuclei and have the shape of biconcave disks. The diameter of erythrocytes varies with different animals.

The nucleated erythrocytes of certain caudate Amphibia are notable among the erythrocytes of other animals for their large size: for example, in the proteus they reach 58 microns in diameter. The erythrocytes of some ruminants are very small: in the goat they are 4 microns in diameter and in the deer—3.6 microns.

The diameter of the human erythrocytes in their natural environment, the plasma, is 8 to 8.5 microns; in dry preparations and on slides it is somewhat smaller (7.2 to 7.7 microns). The human erythrocytes are 2 to 2.5 microns thick. They are very elastic, which enables them to pass through capillaries even when the diameter of the latter is smaller than that of the erythrocytes.

The erythrocytes are very rich in solid substances (up to 37 per cent). The structure of erythrocytes is based on a protein-lipoid stroma which forms a membrane on their surface. In the loops of the stroma there is a solution which contains haemoglobin, salts and some nonelectrolytes.

The membrane of the erythrocytes is impermeable to colloids—proteins and lipoids. It is unequally permeable to ions of mineral salts. The ions of hydrogen, the hydroxyl ions and the other anions—the anions of chlorine, carbonic acid and certain organic acids easily pass through it. The ions of potassium, sodium and calcium permeate through the membrane slowly (potassium ions) or do not pass through it at all (calcium ions). The cation composition of the erythrocytes sharply differs from that of the plasma (Table 3).

Table 3

Content of Certain Ions in the Human Blood Plasma and Erythrocytes

(in mg. per cent)

	$Na^{\cdot}$	$K^{\cdot}$	$Ca^{\cdot\cdot}$	Cl'
Plasma	330	18	10	360
Erythrocytes	90	380	—	205

Haemoglobin is one of the principal anions in the erythrocytes. Owing to this the concentration of the other anions (Cl', HCO_3', etc.) in- and outside the erythrocytes is unequal; their concentration inside the erythrocytes is nearly half that of the surrounding plasma.

Counting the blood corpuscles. Haemocytometers are used in counting the blood corpuscles.

The Bürker haemocytometer and the Goryaev graduated scale (Fig. 5) are manufactured in the U.S.S.R. A rectangular plate bordered on both sides by grooves and divided across is cut in a thick glass slab. Two more plates 0.1 mm. higher are cut out on both sides of the first plate. A drop of blood with a special diluting fluid added is placed on the central plate and is covered by a cover glass which is closely fitted to the outer plates. A layer of diluted blood 0.1 mm. thick is, thus, enclosed between the central plate and the cover glass. The surplus of fluid runs down the grooves surrounding the central plate. Two scales of lines 1/20 mm. apart are engraved on the central plate. Thus, the volume of a layer of fluid corresponding to one square equals $1/20 \times 1/20 \times 1/10 = 1/4{,}000$ mm.^{3} In addition to these small squares Goryaev's scale has large squares each of which corresponds to 16 small ones. The small squares serve to count the erythrocytes, the large ones to count the leucocytes.

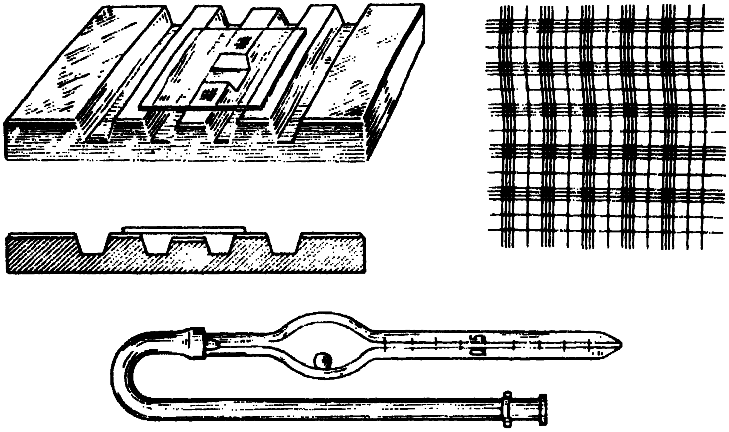


Fig. 5. Bürker's haemocytometer (top and side views) with Goryaev's ruling. Pipette to dilute blood (bottom).

In counting the erythrocytes the blood is diluted 1 : 200 by a special diluting fluid in a 0.9 per cent physiological solution of sodium chloride.

The blood of healthy males contains 5,000,000 erythrocytes per 1 mm.^{3}, that of females—4,500,000. So large a number of erythrocytes offers a very extensive total surface through which oxygen and carbon dioxide diffuse. In man this surface area reaches 3,500 m.^{2}, i.e., it exceeds the surface of the body nearly 2,000-fold.

The number of erythrocytes may vary with different physiological states. Rapid changes are due to redistribution of the erythrocytes in the body. Some of the organs—the spleen, the liver and the skin—act as blood depots retaining the blood corpuscles and giving them back to the blood. The retention of the erythrocytes and their passage into the blood stream is regulated by the nervous system. A marked increase in the number of erythrocytes in the blood is observed during muscular work and under the action of a rarefied atmosphere.

Another reason for changes in the number of erythrocytes, which makes itself felt more slowly, is the change in the rate of their formation or in the rate of their disintegration. In the human adult erythrocytes are formed in the bone marrow. Not only the number of erythrocytes, but also their size, shape and internal composition, may change in blood diseases and may even give rise to erythrocytes with a nucleus.

The changes in shape may be sharply pronounced; the erythrocytes sometimes assume the shape of a pear, a dumb-bell, a bottle, etc. Irregularly shaped erythrocytes are called *poikilocytes*. During increased regeneration erythrocytes with more or less markedly pronounced reticularity, so-called ***reticulocytes***, appear. Erythrocytes with a large diameter are known as ***macrocytes***, those with a small diameter are designated as ***microcytes***. The capacity of erythrocytes for taking different dyes may also change (*polychromatophylic* erythrocytes). Increased activity of the bone marrow gives rise to ***normoblasts*** in the blood; these are cells of the same size as the erythrocytes but with nuclei. ***Megaloblasts***, large nucleated cells containing more haemoglobin than the normal erythrocytes, make their appearance in grave diseases of the blood-forming organs.

A decrease in the number of erythrocytes (*erythropenia*) and a formation of erythrocytes of pathological shapes in the blood are observed during pathological changes in the blood system (anaemia) and during various emaciating diseases. An increase in the number of erythrocytes (*polycythaemia*) occurs in diseases of the blood-forming organs and under the action of a rarefied atmosphere.

Osmotic stability of erythrocytes. When erythrocytes are placed into a hypotonic or a hypertonic medium their volume changes. A considerable increase in the volume is accompanied by *haemolysis*, i.e., the content of the erythrocyte passes into the surrounding solution because of the bursting of the membrane. In haemolysis the blood becomes transparent and is called *laky*. In certain diseases of the blood the stability of erythrocytes in relation to hypotonic solutions changes, and its determination is, therefore, of clinical interest.

To determine the osmotic fragility of erythrocytes a drop of blood is added to sodium chloride solutions of different concentration (from 0.9 to 0.3 per cent). When the liquid has settled, the sodium chloride concentration, in which the first traces of haemolysis appear (minimal resistance), and the concentration in which complete haemolysis begins (maximal resistance), are noted. For healthy people the minimal resistance varies between 0.42 and 0.48 per cent NaCl, while complete haemolysis occurs between 0.3 and 0.32 per cent NaCl.

In addition to osmotic forces haemolysis may be caused by the action of substances which dissolve lipoids (ether, chloroform) or interact with them chemically (digitonin, saponin). The venoms of certain snakes possess haemolyzing properties. Finally, the serum of some animals may have the ability of haemolyzing the erythrocytes of other animals. For example, the serum of hog's blood haemolyzes the erythrocytes of sheep's blood. In some cases, therefore, transfusion of the blood of one animal to another involves a danger for the recipient: the transfused blood is haemolyzed and haemolyzed blood is toxic.

Blood Groups

During man-to-man blood transfusion the blood may be haemolyzed as a result of the action of the specific proteins in the blood of one man on the erythrocytes of the other. This action manifests itself in agglutination of the erythrocytes, while the agglutinated erythrocytes are haemolyzed.

People are divided into four groups according to their agglutination reaction. The existence of four groups is due to the presence of two types of ***agglutinogens*** (A and B) in the erythrocytes and of two types of agglutinins (*α/β*) in the plasma. The erythrocytes may be agglutinated only if A agglutinogen interacts with *α* agglutinin or if B agglutinogen interacts with *β* agglutinin. In some people the erythrocytes do not agglutinate whatever serum be added to them. The erythrocytes of this group *apparently have no agglutinogen at all. In Jansky's classification this group is designated as the first group, and in another classification as Group 0.* At the same time the serum of this group of people agglutinates the erythrocytes of the other three groups which means that it has both agglutinins (α and β). The fourth group is the antithesis of the first group. The serum of the blood of the fourth group is incapable of agglutinating any erythrocytes, i.e., it is completely devoid of agglutinins. The erythrocytes of this group are agglutinated by the serum of all groups, save the fourth, and, consequently, have both A and B agglutinogens. The second group has A agglutinogen in its erythrocytes and β agglutinin in its serum. The blood of the third group contains B agglutinogen in its erythrocytes and α agglutinin in its serum. Thus, when the erythrocytes and serum of different people, though belonging to the same group, are mixed there can be no agglutination because the interacting agglutinin and agglutinogen cannot meet. Table 4 shows when agglutination takes place and when it is impossible. The method for determining the blood groups is illustrated in Fig. 6.

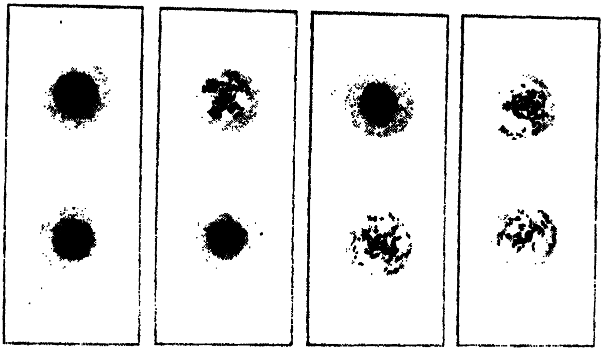


Fig. 6. Blood grouping by agglutination methods. Agglutinated erythrocytes form clusters visible to naked eye.

Left to right: reaction of blood of first, second, third and fourth groups resulting from mixing a drop of blood of each group with a drop of serum belonging to people having second blood group (lower part of figure) or third blood group (upper part of figure). Blood of first group is not agglutinated; blood of second group is agglutinated when serum from third blood group is added (agglutination above); blood of third group is agglutinated when serum from second blood group is added (agglutination below); blood of fourth group is agglutinated by serum of both second and third blood groups.

Usually the *recipient* is transfused much less blood than he has. The transfused blood is, therefore, strongly diluted by his own blood, the concentration of the transfused agglutinins proves low and the agglutinins are incapable of agglutinating and haemolyzing the recipient's erythrocytes. Nevertheless, if the transfused erythrocytes have an agglutinogen which corresponds to the agglutinin in the recipient's plasma they are agglutinated and haemolyzed.

Table 4

Blood Groups after Jansky

(agglutination resulting from mixing the serum and erythrocytes of the groups indicated in the table is marked by a + and nonagglutination by a —)

Serum and its agglutinins	Erythrocytes and their agglutinogens			
	1st group (0)	2nd group (A)	3rd group (B)	4th group (AB)
1st group ($\alpha\beta$)	—	+	+	+
2nd group (β)	—	—	+	+
3rd group (α)........	—	+	—	+
4th group (0)	—	—	—	—

Haemolysis liberates toxic products (adenosine triphosphoric acid, in particular) which cause grave disorders and may lead to death. Thus, the people of the first blood group (plasma $\alpha\beta$) may be transfused blood of only the first group (erythrocytes 0). The people of the second blood group (β plasma) may be transfused the blood of the first (erythrocytes 0) and of the second (erythrocytes A) groups. In the third blood group (α plasma) the donors may belong to the first (the erythrocytes contain no agglutinogen) and the third (the erythrocytes have B agglutinogen) groups. The people of the fourth group (the plasma contains no agglutinin) may be given the blood of any group. The people of this group may, therefore, be called *universal recipients*. Contrariwise, the people of the first blood group may be called *universal donors* because their blood may be transfused to any person without risking haemolysis of the transfused erythrocytes provided the plasma of the transfused blood does not contain a large amount of agglutinins and not much blood is transfused.

The blood group is retained throughout the individual's life independent of age and disease.

Substantial progress has recently been made in studying the chemical nature of the agglutinogens. The composition of agglutinogens includes polysaccharides which contain amino sugar and glucuronic acid. It has been found that these polysaccharides reside not only in the erythrocytes; they are also encountered in other cells, as well as in the saliva, in the gastric mucosa, etc. The composition of the agglutinogens is apparently very diverse and in addition to A and B agglutinogens there are several others (M, N, P) which are, however, unimportant in blood transfusions.

The agglutinogen known as the Rhesus factor (Rh factor) is of practical interest. The name is borrowed from the marmoset (*macacus rhesus*). If the erythrocytes of the marmoset are injected into the blood of a rabbit the serum of this rabbit acquires the ability to agglutinate these erythrocytes, as well as the erythrocytes of the majority (86 per cent) of people (rhesus-positive people). Fourteen per cent of the people (rhesus-negative people) lack this factor. Repeated injections of erythrocytes of Rh-positive people into the blood of Rh-negative people may, despite the A and B agglutinogen compatibility of the blood, haemolyze the injected erythrocytes because of a formation of anti-Rh agglutinins. Since this factor is inherited the Rh factor assumes particular importance during pregnancy. With a Rh-positive father and a Rh-negative mother the foetus may turn out to be Rh-positive. Since the erythrocytes of the foetus may penetrate into the mother's blood, the latter will develop anti-Rh agglutinin. Penetrating into the blood of the foetus through the placenta it will cause destruction of erythrocytes and anaemia and may thus destroy the foetus. On the other hand, if an Rh-negative woman is transfused the blood of an Rh-positive donor during delivery the woman may die because of the destruction of the transfused erythrocytes.

The agglutinins are proteins which form part of the γ-fraction of globulins.

In many cases the plasma may be successfully transfused instead of the whole blood. During extensive haemorrhages it is first of all necessary to replenish the total amount of fluid in order to maintain the blood pressure. Because of the oncotic pressure they produce, the proteins of the plasma are capable of retaining the fluid in the blood stream.

The presence of agglutinins in the plasma makes it necessary to transfuse erythrocytes compatible with the recipient's plasma, i.e., from a person of the corresponding group. The specific properties of the proteins are lost, however, when they are denatured. The method of processing serum which leads to the loss of the immuno-biological properties by the proteins is based on protein denaturation. Human beings may be safely transfused such serums even when the latter are taken from animals. The great value of this method consists in the fact that, unlike whole blood, which can be preserved for only a short time, serum can be kept indefinitely, while the sources for obtaining animal serum are practically unlimited.

Erythrocyte Sedimentation Rate

If substances which prevent coagulation are added to the blood the corpuscles can be separated from the plasma by simple precipitation. The determination of the erythrocyte sedimentation rate has acquired diagnostic importance in medical practice. The reaction of erythrocyte sedimentation is considerably accelerated in pregnancy, tuberculosis and different inflammations. The difference in the rate of sedimentation is due to the fact that the erythrocytes do not agglutinate at the same speed. In the beginning the erythrocytes group themselves in rouleax (rolls), then they form small lumps. The latter precipitate rapidly. The differences in the rate of agglutination are due to the differences in the electric charges of the plasma proteins.

The erythrocyte sedimentation rate is usually determined by means of Panchenkov's device which consists of four graduated capillary tubes placed in an upright frame. To prevent coagulation the blood is mixed with a sodium citrate solution and aspirated into the capillary tubes which are placed vertically. After a certain lapse of time the column of the plasma above the erythrocytes is measured. In healthy people the column measures 4 to 10 mm. per hour, in women this value is, as a rule, higher than in men.

Haemoglobin

The main mass of the dense substances of the erythrocytes consists of haemoglobin, a pigment of the blood. It comprises 32 per cent of the erythrocytes and 14 to 16 per cent of the whole blood. Haemoglobin is a complex protein with a molecular weight of about 68,000. The protein part of haemoglobin is called *globin,* the nonprotein or haemin group is known as the *haem.* A compound of four haem molecules with native, i.e., unchanged, globin is haemoglobin with the globin making up 96 per cent of the total weight of haemoglobin. Haemoglobin easily dissolves in water.

Crystals of oxyhaemoglobin, differing in shape in various animals, can be obtained from a water-alcohol solution in the presence of oxygen.

M. Nentsky and his pupils made an important contribution to the studies of the chemical structure of the haemin group of haemoglobin. The haemin group includes one atom of bivalent iron oxide and a porphyrin group of four pyrrole rings with side chains. An oxidized haem is called *haematin.* The crystals of an oxidized hydrochloric haem are known as *Teichmann crystals.* Because of their characteristic appearance the latter may be used in determining the presence of haemoglobin; this fact is used in forensic medicine to ascertain the presence of blood.

A haem may enter into combination with most diverse nitrogenous bodies—amines, amino acids, hydrazine, pyrrole, pyridine, nicotine and, finally, with proteins. Because of their ability to absorb light in the yellow-green part of the spectrum all these compounds yield strongly coloured solutions. These substances are, therefore, commonly termed *haemochromogens*. Their solutions are coloured yellow-brown or red. The haemochromogens also include haemoglobin which has a characteristic spectrum. One molecule of haemoglobin contains four haemin groups. The haemoglobin derivatives—its compound with oxygen (*oxyhaemoglobin*), with carbon monoxide (*carboxyhaemoglobin*) and the product of haemoglobin oxidation (*methaemoglobin*)—also have characteristic spectra: these derivatives can be distinguished from each other by their absorption bands (Fig. 7).

Haemochromogen formerly implied the nonprotein part of the haemoglobin which split off from the latter under the action of weak acid and alkaline solutions. It has now been established that a mere addition of weak acid and alkaline solutions does not suffice to divide the haemoglobin into protein and nonprotein parts, and that what was considered haemochromogen is a compound of the haem and denatured protein.

The chemical structure of the haem is the same whatever the animal from whose haemoglobin it is obtained, though the properties of the haemoglobins isolated from the blood of different animals are not exactly

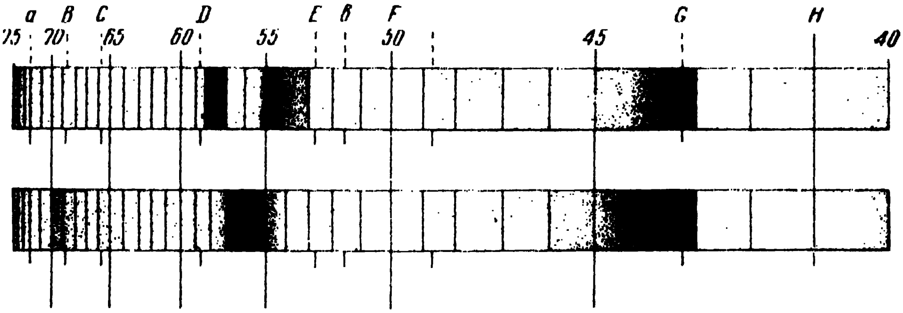


Fig. 7. Absorption bands in spectra of oxyhaemoglobin and reduced haemoglobin.

alike. The haemoglobins of various animals differ from each other in the shape of their crystals, in the position of the absorption bands and, especially, in the force with which they combine with oxygen. The haemoglobin in the blood of an adult animal differs from that in the blood of the foetus. The bond of the haemoglobin with oxygen is stronger in the human foetus than it is in the human adult. All these differences in the properties of haemoglobin are due to the differences in the protein part, i.e., the globin.

A remarkable property of haemoglobin is its ability to form weak, easily dissociating, compounds with certain gases, primarily with oxygen. The compound of haemoglobin and oxygen is known as *oxyhaemoglobin*. One molecule of haemoglobin can unite with 4 molecules of oxygen, i.e., with as many molecules as there are particles of haem or atoms of iron in the haemoglobin. Meantime, the iron of the haemoglobin remains in a bivalent state. The reaction between haemoglobin and oxygen is reversible. As the oxygen concentration rises the equilibrium shifts towards an increase in the amount of oxyhaemoglobin; as the oxygen concentration drops the equilibrium shifts towards an increase in the amount of reduced haemoglobin. Since the concentration of oxygen in a solution is directly proportional to the partial pressure (tension) of oxygen the oxygen tension is the principal factor influencing the percentage of haemoglobin oxygenation. Besides, this equilibrium is also influenced by the temperature and the reaction of the environment (see p. 201).

As the haemoglobin changes to oxyhaemoglobin its optical properties also change (Fig. 7). Reduced haemoglobin has a wide absorption band in the yellow-green part of the spectrum, nearly halfway between the *D* and *E* lines, with a maximal absorption at a 555 mμ wave. Oxyhaemoglobin has two absorption bands divided by a light interval in the same part of the spectrum; in one of these bands maximal absorption is observed near line *D* (577 mμ), in the other—closer to line *E* (541 mμ). Correspondingly, the blood turns scarlet when oxygenated and grows darker and lilac-tinged when giving off its oxygen.

In addition to the role of oxygen transporter haemoglobin plays the part of a buffer which maintains the constancy of the blood reaction. Besides, oxyhaemoglobin possesses more sharply pronounced acid properties than does haemoglobin. The carbonic acid is, therefore, displaced from the bicarbonates when haemoglobin changes to oxyhaemoglobin.

I. Sechenov discovered the ability of haemoglobin also reversibly to combine with carbon dioxide.

Carboxyhaemoglobin, the compound of haemoglobin and carbon monoxide, very much resembles the compound of haemoglobin and oxygen. The optical properties of carboxyhaemoglobin differ very little from those of oxyhaemoglobin. The reaction between haemoglobin and carbon monoxide is also reversible and the saturation of haemoglobin with carbon monoxide depends on the partial pressure of the latter. The essential difference, however, lies in the fact that carboxyhaemoglobin is a much stabler compound than oxyhaemoglobin. Carboxyhaemoglobin dissociates 300 times as slowly as oxyhaemoglobin. Therefore, if air containing 20.8 per cent oxygen and 0.07 per cent coal gas is inspired, half the haemoglobin of the arterial blood will change to oxyhaemoglobin and the other half will change to carboxyhaemoglobin. With a higher content of coal gas nearly all the haemoglobin is bound by carbon monoxide and the blood can no longer transport oxygen, which leads to oxygen starvation of the tissues. This explains the harmful effect of carbon monoxide.

Reduced haemoglobin, like oxyhaemoglobin and carboxyhaemoglobin, contains a haem with bivalent iron (iron oxide). By acting on it with certain substances (potassium ferricyanide, nitrites, etc.) it is possible to transfer the haem iron, which forms part of the haemoglobin, into ferric oxide, i.e., the trivalent form. This haemoglobin derivative is known as ***methaemoglobin.*** Methaemoglobin colours the blood chocolate. The reaction may be schematically represented as follows:

$$\underset{\substack{\text{oxyhaemoglobin + water +}\\ \text{+ potassium ferricyanide}}}{HbO_2 + H_2O + K_3Fe(CN)_6} \rightarrow \underset{\substack{\text{methaemoglobin + oxygen +}\\ \text{+ yellow blood salt}}}{HbOH + O_2 + K_3HFe(CN)_6}$$

Methaemoglobin cannot reversibly combine with oxygen and, consequently, cannot serve to transport oxygen. Injection of appreciable amounts of methaemoglobin-producers into the blood rapidly destroys the organism. However, if the organism does not die during the very first hours after part of the haemoglobin has changed to methaemoglobin the latter is again reduced to haemoglobin. Under these circumstances the reduction of haemoglobin involves enzymes (dehydrases) and is effected at the expense of simultaneous oxidation of lactic acid and glucose.

One of the properties of methaemoglobin is its ability to combine with hydrocyanic acid and yield cyanmethaemoglobin. Owing to this the animal in which part of the haemoglobin has changed to methaemoglobin offers greater resistance to hydrocyanic acid poisoning than a normal animal.

The amount of haemoglobin in the blood is estimated either by the amount of oxygen it binds, or by the amount of iron it contains; it is also measured by the intensity of the coloration conditioned either by the haemoglobin itself or by haematin (colorimetric methods).

To estimate the amount of haemoglobin by the first method the haemoglobin is changed to oxyhaemoglobin by shaking the blood in the presence of air. The oxyhaemoglobin is then changed to methaemoglobin by an addition of potassium ferricyanide; at this time all the oxygen loosely combined with the haemoglobin is liberated. The amount of liberated oxygen is measured in Van Slyke's or Barcroft's apparatus. One gram of haemoglobin corresponds to 1.34 ml. of oxygen at 0° C and 760 mm. pressure.

The simplest colorimetric method of estimating the haemoglobin content of the blood is the Sahli method. 20 mm.^{3} of blood is taken by means of a micropipette and is diluted with decinormal HCl to mark 10 in a small graduated beaker. Haemoglobin breaks up into globin and haem and the latter, in the presence of oxygen, changes to haematin which colours the solution light brown. The colour of the solution is compared with a standard solution kept in sealed beakers of the same diameter. The mixture is diluted with distilled water until the colour of the test matches that of the standard. The higher the content of haemoglobin in the blood the more must the test blood be diluted. The beaker has graduations which show by the volume of the fluid the haemoglobin content in per cent to the norm. According to Sahli's method 100 per cent haemoglobin corresponds to 17.3 gr. of haemoglobin per 100 ml. of blood. As before stated, in most people the haemoglobin content is lower, constituting 80-90 per cent and, estimated according to Sahli's method, corresponds to 14-16 gr. of haemoglobin per 100 ml. of blood.

Leucocytes and Thrombocytes

Leucocytes. There are much fewer white blood corpuscles, or so-called leucocytes, than erythrocytes. 1 mm.^{3} of adult blood contains from 5,000 to 8,000 white blood corpuscles.

The leucocytes are counted in haemocytometers by the same method as the erythrocytes. To count the leucocytes the blood is diluted 1 : 10. To facilitate the count the fluid used to dilute the blood is a 3 per cent acetic acid which haemolyzes the erythrocytes and leaves the leucocytes intact.

Leucocytes differ in shape, size, the ratio between the volume of the cytoplasm and the nucleus, the ability to stain and the shape of the nucleus. The group of agranulocytes includes the large and small lymphocytes and monocytes.

The second group consists of granulocytes which are, in turn, divided into neutrophil, basophil and eosinophil leucocytes.

Leucocytes are produced in lymph nodes (lymphocytes and monocytes), in the spleen (lymphocytes and monocytes) and in the bone marrow (granulocytes). They do not live long—only a few days. A temporary increase in their number is known as *leucocytosis* and is observed after meals (digestive leucocytosis), after muscular work and especially in acute inflammations. It has been shown that changes in the number of leucocytes involve the central nervous system. By combining formerly indifferent stimuli with the action of factors which cause leucocytosis it is possible to develop a conditioned-reflex leucocytic reaction of the body to the formerly indifferent agent. The disease in which a marked and stable increase in the number of leucocytes occurs is called *leukaemia*. In some diseases, for example in typhoid fever, a decrease in the number of leucocytes in the blood is observed; this condition is known as *leucopenia*.

Not only the total number of leucocytes, but also the correlation among their different forms, varies in different diseases. Determination of this correlation, known as the *differential count*, is of great diagnostic importance. For example, a neutrophil leucocytosis is a symptom of inflammation. Thus, an increase in the number of eosinophils is observed in diseases connected with the presence of parasites (echinococci, intestinal worms). An increase in the number of lymphocytes is noted in certain forms of infectious tonsillitis (lymphocytic tonsillitis). Young and pathological forms of leucocytes appear in a number of diseases of the blood and in certain malignant tumours.

Role of leucocytes. The physiological significance of leucocytes is not sufficiently clear as yet. Leucocytes are rich in enzymes which are capable

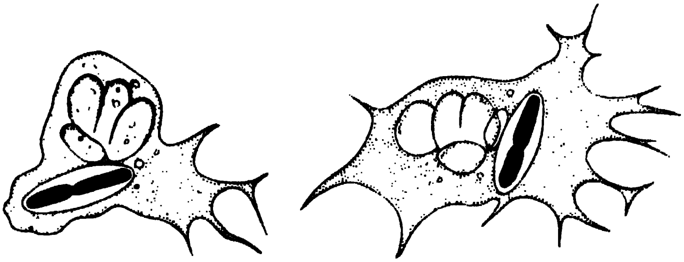


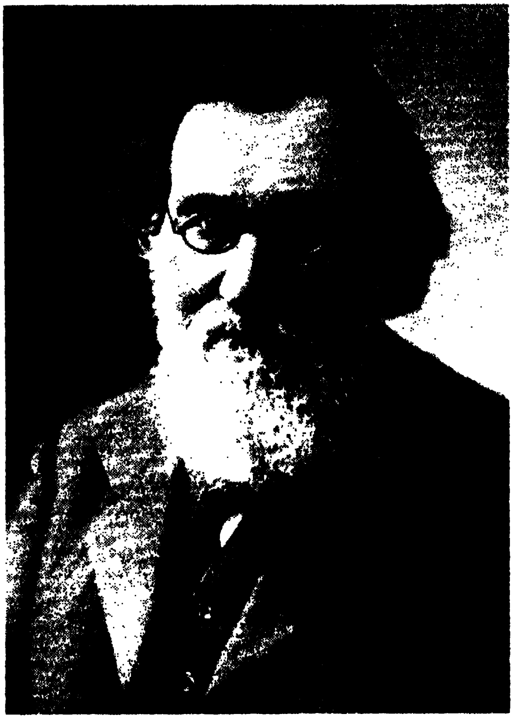
Fig. 8. Phagocytosis of bacteria by leucocytes of the frog (after I. Mechnikov).

of splitting various substances. One of the main functions of leucocytes is to protect the organism from bacteria and foreign bodies which penetrate into the blood and the tissues. Leucocytes are also of essential importance in reconstruction of the tissues since they ingest (and digest) the particles which break off from disintegrating tissues.

Unlike the erythrocytes, which are passively carried by the blood stream, leucocytes are capable of independent movement. In studying capillaries in transparent tissues under the microscope we can see individual leucocytes adhere to the wall of the capillary and after a certain lapse of time penetrate into the surrounding tissue at points of junction of endothelial cells (migration of leucocytes). If some foreign body finds its way into a tissue a large number of leucocytes rush at it from the blood vessels. If the foreign body is small the leucocytes devour it (Fig. 8). What follows depends on whether the leucocytes are capable of splitting this substance with their own enzymes and, thus, of digesting it. In the first case the captive substances are subjected to intracellular digestion and disappear. This happens not only to particles of fat and protein and to dead cells, but also to microorganisms. The doctrine of the important protective role of the leucocytes consisting in devouring the microbes was advanced and elaborated by I. Mechnikov. The cells which ingest dead and living particles he named *phagocytes*, while the ingestion of these particles by the cells he termed *phagocytosis*. When the microorganisms are easily ingested and subsequently destroyed by the leucocytes the body rapidly rids itself of the infection. This promotes *immunity* to infection. In addition to the leucocytes circulating in the blood some fixed cells of the spleen, the liver (Kupffer's cells) and the cells of the so-called reticuloendothelial tissue also possess phagocytic ability.

When the granules of a substance (for example, grains of indissoluble dyes, coal, etc.) ingested by the leucocytes cannot be split the leucocytes come out to the surface of the mucous membranes with them whence they can be removed from the body together with the ingested material and desquamated cells. Finally, if the foreign body is too large or produces toxins the leucocytes accumulated around it disintegrate. Their enzymes destroy the surrounding tissue and an abscess is formed.

I. Mechnikov demonstrated that in addition to their protective function the phagocytes also take part in rebuilding the morphological structure of the tissues. A dying cell is subjected to phagocytosis. For example, as the tadpole changes to a frog phagocytes accumulate in the tail where they dissolve and ingest cells and muscle fibres. In tissue injuries or burns the remains of the destroyed cells are ingested by leucocytes which rush to the site of injury. The movement of leucocytes towards destroyed cells or foreign bodies is due to the fact that the latter liberate chemical substances towards which the leucocytes move because of their positive *chemotaxis* (ability to move towards a chemical stimulus). Finally, the phenomenon of phagocytosis may play an essential part in the processes of absorption and transport of certain substances. During digestion the mucosa of the alimentary canal abounds in leucocytes.



I. Mechniko

The thrombocytes, or Bizzozero platelets, are small easily disintegrating disks owing to which their structure is not yet clear. They are formed in the bone marrow during disintegration of the giant cells known as the megacaryocytes. Thrombocytes are found only in the blood of mammals. The blood of birds and of the lower vertebrates does not contain them. There are about 400,000 of them in each cubic millimetre of human blood. Thrombocytes are rich in thrombokinase. In injuries to the vessels and in haemorrhages the easily disintegrating thrombocytes, apparently, form the centres around which coagulation of the blood begins. The thrombocytes are destroyed in the spleen. In some diseases the number of thrombocytes decreases. This condition is usually designated as ***thrombopenia***. Retarded blood coagulation is noted in cases of marked thrombopenia.

CHAPTER 7

REGULATION OF THE BLOOD SYSTEM

Regulation of the Blood Composition

The blood is a fluid tissue which by circulating throughout the body brings all the organs into humoral contact with each other.

Changes in the composition of the blood exert a great influence on the metabolism and on the functional state of all the organs of the body. The flow of nutritive substances and oxygen to the tissues, as well as the removal of the unnecessary or harmful products of metabolism, depend in certain measure on the composition of the blood. The acid-base balance and the osmotic phenomena, which are accompanied by passage of water from the blood stream into the tissues and back, also depend on the composition of the blood. The higher the organization of the animal the more sensitive are its vital organs (brain, heart, liver, etc.) to deviations of the blood from its normal composition. This was noted 70 years ago by Claude Bernard who made the following statement: "The constancy of the internal environment is the basis for the free life of the organism." This "constancy of the internal environment" implies the definite physicochemical properties of the blood, lymph and tissue fluids necessary for the existence of the cellular and extracellular structures. The total molecular concentration and the value of the osmotic pressure connected with it, the total concentration of electrolytes and the concentration of individual ions, the acid-base balance, the content of nutritive materials and products of intermediate and final metabolism in the blood are all maintained on a definite level, deviations from which occur within relatively narrow limits. This "constancy" is maintained by mechanisms which have arisen and have developed during the phylogenesis and which regulate the composition of the blood and moderate its deviations from the normal. The higher the organization of the animal the more perfectly is the "constancy of the internal environment" maintained.

The definite composition and properties of the blood are maintained by the activity of the nervous system which continuously influences the passage of nutritive substances into the blood, the elimination of the products of metabolism from the blood into the surrounding medium, the exchange of substances between the blood and the tissues, the intensity of metabolic processes in the tissues and, finally, the very formation of the blood constituents.

Thus, Claude Bernard's words cannot be interpreted, as they sometimes are interpreted by certain foreign scientists, as a thesis of autonomy of the internal environment from the action of the external environment and of an absolute constancy of the properties of the blood. External influences may produce more or less sharp changes in the composition and the properties of the blood because of the alterations they cause in respiration, perspiration, urine production and metabolic processes. But due to the reflex acts which occur in response to these changes and which are effected through the central nervous system the changes in the composition of the blood are normally rapidly equalized.

Changes in the composition and the properties of the blood, the passage of nutritive materials into the blood and the transport by the blood of these substances, formed as a result of metabolism in the various organs, exert an essential influence on the functional state of the different physiological systems. These changes involve the central nervous system and the activity of the latter may, thus, considerably influence the functions of the different organs not only directly, but also by alterations in the composition of the blood which take place under its regulatory influence. Of special importance in this is the transport by the blood of certain active substances, *hormones*, which are formed in the glands of internal secretion.

Metabolism of Erythrocytes, Their Formation and Longevity

The mature erythrocytes of the lower vertebrates contain a nucleus and possess well developed oxidative metabolism. The erythrocytes of mammals do not contain a nucleus and hardly consume any oxygen. Their metabolism manifests itself in glycolysis, i.e., in the splitting of sugar to lactic acid involving a number of phosphoric compounds. In addition to the numerous enzymes necessary for the intermediate reactions of metabolism—the reactions of glycolysis—the erythrocytes also contain such enzymes as phosphatase, cholinesterase, catalase, etc. The hexosophosphates and the triosophosphates, as well as the adenosine triphosphoric acid are continuously renewed during glycolysis. The use of tracer, i.e. radioactive, phosphorus has made it possible to ascertain that the phosphorus of the lipoids and of the phosphorus-containing proteins of the erythrocytes are slowly renewed (G. Vladimirov and associates). Thus, even in the non-nucleated erythrocytes of man and the higher animals we can discover the most characteristic manifestations of life—processes of metabolism and a renewal of the constituents of cellular structure.

At the early stages of embryonic development the erythrocytes are formed in the embryonic mesenchyme of the allantoic sac. They are formed from the internal portions of the folds of the mesenchyme simultaneously with the walls of the vessels, the latter being formed from the external cells. These vessels make up the network connected with the vessels of the chorion and with the heart. The erythrocytes contain a nucleus and are very large (erythroblasts, megaloblasts). By the end of the fourth month of foetal development the blood no longer forms in this manner. In the second and third months the blood is mainly formed in the liver, later also involving the spleen. Non-nucleated erythrocytes are formed in these organs. In the fifth month blood begins to be formed in the bone marrow.

In healthy adults the bone marrow is the only place where the erythrocytes are formed and where they mature. The wide capillaries of the bone marrow contain considerable numbers of erythroblasts, nucleated cells from which nuclear cells containing haemoglobin are formed at first and after the nucleus is lost (part of the nucleus is dissolved and the rest is ejected) anuclear erythrocytes are formed. If the formation of blood is accelerated the complex erythrocyte maturation cycle is slower than the rate at which they enter the blood, and the blood stream receives immature erythrocytes containing a nucleus—normocytes and normoblasts. The processes of blood formation are disturbed when the body is inadequately supplied with proteins and certain vitamins—vitamin B_{12}, pyridoxine and folic acid (see Chapter 32).

The average lifetime of individual erythrocytes is estimated by using tracer atoms.

The haemoglobin inside the erythrocytes is not renewed and is eliminated from the blood stream together with the erythrocytes. Glycocol is used for the synthesis of the pyrrol groups of the porphyrin ring of the haem. If glycocol, enriched by the heavy isotope of nitrogen (N^{15}), is added to the food new erythrocytes are formed in the bone marrow with haemoglobin traced in the haem by the isotope. By periodically determining the content of the heavy isotope of nitrogen in the haem it is possible to estimate how long the erythrocytes, formed when the tracer glycocol was consumed, have resided in the blood. It has been found with the aid of this method that the human erythrocyte lives an average of about 130 days, i.e., much longer than formerly believed (from 3 to 4 weeks). Following the destruction of the erythrocytes the haemoglobin is also destroyed. The haemin group is transformed into bile pigments—bilirubin and biliverdin.

It is possible to preserve the erythrocytes for some time in conserved blood. Various media have been proposed for preserving the blood; these contain certain salts, sugar (glucose and saccharose), sodium citrate to prevent coagulation, and certain antiseptics to inhibit the development of incidental bacteria. The blood is kept at a low temperature (4 to 6° C). Despite all precautions the conserved blood gradually changes—the glucose is consumed, lactic acid is accumulated, the reaction of the blood grows more acid, potassium passes from the erythrocytes into the plasma and partial haemolysis begins. Conserved blood is suitable for transfusion for about one to one and a half months.

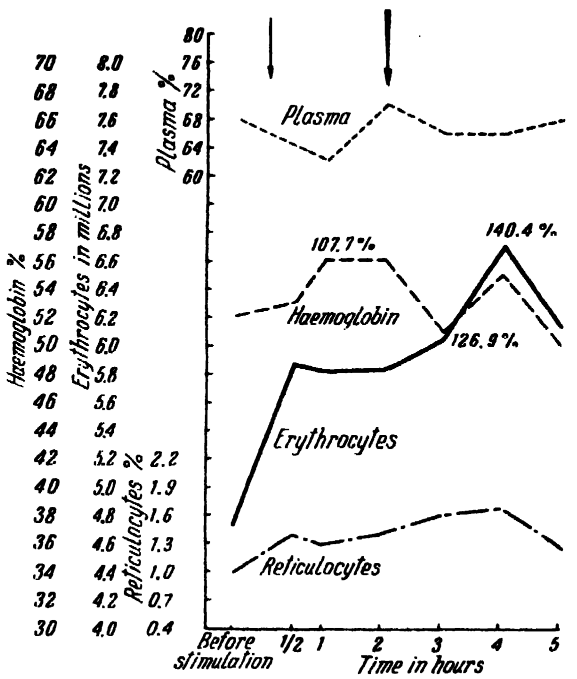


Fig. 9. Effect of stimulating (its beginning and end are shown by arrows) interoceptors in the cat's stomach on amount of plasma, haemoglobin, erythrocytes and reticulocytes.

Interoceptors were stimulated by inflation of rubber balloon inserted into stomach through fistula, according to V. Chernigovsky and A. Yaroshevsky (data furnished by Y. Kan).

Regulation of the Activity of the Organs Involved in the Formation, Distribution and Destruction of the Blood Corpuscles

The content of corpuscles in the blood is regulated by the activity of a number of organs which form, distribute and destroy the blood. The system of these organs was defined by G. Lang as the "blood system." This system includes the bone marrow, the lymph nodes, the spleen and the liver. The erythrocytes are formed and mature in the bone marrow; the granulocytes and the thrombocytes are also formed in the bone marrow. The lymphocytes are formed in the lymph nodes and the malpighian bodies of the spleen. The outworn erythrocytes are destroyed in the reticuloendothelial tissue of the spleen. Destruction of erythrocytes accompanied by the formation of bile pigments from the haemoglobin also takes place in the liver. The *ferritin* of the spleen and. especially, of the liver contains iron reserves used by the body in building new particles of haemoglobin. The spleen and the liver take part in redistributing the blood corpuscles.

All of the aforesaid organs have been found to have effector innervation: their function is controlled by the central nervous system. This problem has been especially studied by V. Chernigovsky and his associates at the Pavlov Physiological Institute. It has been shown that the injection of certain chemical stimuli into the vascular system of the spleen which has retained only nervous connections with the body produces powerful circulatory and respiratory reflexes. The presence of chemoreceptors in the liver, the bone marrow and the lymph nodes has also been demonstrated. Stimulation of the mechanoreceptors of the stomach during its distension by a balloon inflated in the stomach alters the number of erythrocytes and other blood corpuscles (Fig. 9).

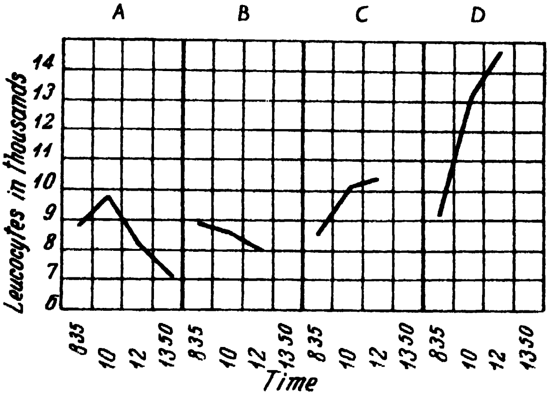


Fig. 10. Disappearance and gradual restoration of digestive leucocytosis in the dog after change in functional state of cerebral cortex caused by collision, i.e., use of conditioned stimulus which provokes inhibition immediately after positive digestive conditioned stimulus.

A—3rd day; *B*—6th day; *C*—21st day; *D*—25th day after "clash" (after V. Chernigovsky and A. Yaroshevsky).

The connection of these organs with the central nervous system, like that of all the other organs of the body, is bilateral. It ensures both the transmission of the impulses, which arise in the receptors of these organs, along the afferent fibres to the centres and the reverse—the action of the impulses, which run along the efferent fibres from the centres, on these organs. The existence of bilateral nervous connections between the organs of the blood system and the central nervous system results, on the one hand, in that reflexes to other systems of the body arise in these organs and, on the other hand, in that changes in the composition of the blood can be produced by stimulation of various receptor fields in the body. Thus, anaemia was produced in animals by action on certain portions of the gastric mucosa and on the carotid sinus with the additional severance of the depressors, etc. Observations of a patient with a blood disease conducted in S. Botkin's clinic and later in G. Lang's clinic testify to the fact that maturation of erythrocytes and their passage into the blood are dependent on the nervous system. The investigations of K. Bykov's associates have demonstrated changes in the blood-filling of organs under the influence of conditioned reflexes which, as is well known, involve the cerebral cortex. It has been found possible to provoke leucocytosis by conditioned-reflex influences. It has also been shown that an impairment of the functions of the cerebral cortex after clashing the positive and inhibitory processes (Chapter 36) leads to a disappearance of the digestive leucocytosis for several days (Fig. 10).

The Pavlov principle of nervism, thus, finds vivid confirmation also in relation to the blood system.

CHAPTER 8

THE LYMPH

Tissue Fluid

Only in certain organs (the liver and the lungs) do the cells directly adjoin the walls of the blood capillaries. In addition to the endothelium of the capillaries a number of other organs have an intercellular substance between the blood and the cells. This substance consists of fibres of connective tissue (collagenous and elastic fibres), homogenous material of a protein nature and intercellular spaces filled with tissue fluid. In addition to the intercellular spaces there are also cavities (the pericardial cavity, the pleural cavity, the abdominal cavity, the central canal of the spinal cord, the cerebral ventricles, the cavities of the joints, etc.) filled with a serous fluid.

The tissue fluid continuously exchanges substances with the blood. The main factors capable of causing the passage of fluid from the blood stream into the tissues and back are: 1) a difference in osmotic pressure between the tissue fluid and the blood and 2) hydrostatic pressure of the blood in the capillaries.

The value of osmotic pressure is determined by the summary molecular concentration independent of the size and electric charge of the particles. The ions of electrolytes, the undissociated molecules of crystalloids and the colloid particles are osmotically active. The osmotic pressure in the blood plasma is approximately 7.6 atmospheres. The tissue fluid has nearly the same osmotic pressure. The difference in osmotic pressure, which for some reason or other arises between the blood plasma and the tissue fluid, can rapidly be equalized because of the high permeability of the capillary walls to the low molecular compounds—sodium chloride and other mineral substances, glucose, urea and other products of metabolism—dissolved in the plasma and in the tissue fluid. Nevertheless, when dissimilation, which leads to the formation of products of carbohydrate, protein and fat conversion, proceeds intensively, the total molecular concentration in the cells and in the tissue fluid rises above that in the blood plasma. The resulting difference in osmotic pressure between the plasma and the tissue fluid is the reason for the passage of water from the former into the latter. Such enrichment of the organs with water at the expense of the blood occurs during their increased activity, for example, during muscular work and *during the secretory activity of the glands.*

When the organs work uniformly and crystalloids easily penetrate through the capillary walls the osmotic pressure conditioned by these substances in the plasma and the tissue fluid is equalized. The content of colloids, primarily proteins, in these fluids is, therefore, of special importance in the distribution of water between them. Colloids permeate the wall of the capillaries with difficulty. Since the blood plasma contains much more proteins than the tissue fluid there is a difference of osmotic pressure between them.

The osmotic pressure conditioned by the plasma colloids is called *colloid osmotic* or *oncotic* pressure. In view of the high molecular weight and, consequently, low molecular concentration of the proteins their colloid osmotic pressure is low—15 to 20 mm. Hg. The oncotic pressure of the blood plasma is a factor which aids in the passage of water from the tissues into the blood stream.

The oncotic pressure is resisted by the pressure which acts on the blood in the capillaries, i.e., the hydrostatic pressure of the blood. The blood pressure in the arterial part of the capillaries reaches about 25 to 35 mm. Hg and, consequently, exceeds the colloid osmotic pressure of the plasma. In the initial portion of the capillaries the fluid, therefore, passes from the blood into the tissue which surrounds the capillaries. Contrariwise, at the venous end of the capillaries the hydrostatic pressure of the blood is already lower than the colloid osmotic pressure and the water passes from the tissue fluid back into the blood. The blood, thus, continuously exchanges substances with the tissue fluid. Experiments, in which heavy water was injected into the blood of the guinea-pig, have shown that about 3/4 of the entire water of the blood passes from the blood stream into the extracellular fluid and back per minute.

Under normal physiological conditions the total amount of water passing from the blood into the tissues will correspond to the amount of water passing from the tissues into the blood. With a drop in the oncotic pressure more water passes from the blood into the surrounding tissues and the latter become oedematous. For example, during perfusion of isolated organs with saline solutions these organs swell up. Oedema of a number of systems and organs also develops as a result of protein impoverishment of the blood plasma during protracted protein starvation of the organism.

The Lymph and Its Composition

The lymph is formed from tissue fluid which penetrates into the lymphatic capillaries. The latter are isolated portions of intercellular space separated by a thin layer of endothelial cells. As the lymphatic capillaries anastomose they grow larger and form lymphatic vessels. Penetrating into the lymph spaces the tissue fluid flows slowly, passes through the lymph nodes, acquires white blood corpuscles and assumes the character of the fluid known as the *lymph.*

The lymphocytes are formed in the lymph nodes. In the lymph nodes, too, the solid particles suspended in the lymph are retained. The lymphatic vessels drain into the thoracic duct whence the lymph enters the venous blood.

The composition of the lymph is close to that of the blood plasma. The content of salts and of the nitrogenous and non-nitrogenous products of metabolism is nearly the same as in the blood plasma. However, changes in metabolism in the organs produce sharper variations in the composition of the lymph than in that of the blood. This is due to the proximity of the lymph to the cells and to the slow flow of the lymph. The lymph contains much fewer protein bodies than the plasma. The content of protein in the serous fluids which fill the body cavities is negligible and amounts to tenths of one per cent. The lymph collected from the lymphatic vessels and, especially, from the thoracic duct already contains much more protein (from 0.3 to 5 per cent) which, moreover, includes albumins and globulins.

The composition of the lymph drained from the intestinal villi varies considerably. As the intestines absorb the nutritive substances the fats pass into the lymph spaces of the villi. The drained lymph is rich in fats (up to 3 or 4 per cent). has a whitish appearance and is called the lactic juice (chyle).

Lymph Formation and Flow

The amount of lymph formed varies with the passage of fluid from the blood into the tissues and back. An increase in the amount of tissue fluid leads to an increase in lymph formation. Lymph formation is in large measure dependent on the size of the surface and on the permeability of the capillary walls. The capillaries of the liver and of the intestines are known to be especially permeable. As the capillary pressure in these organs rises the amount of lymph formed increases manyfold. The permeability of capillaries increases when the tissues are inadequately supplied with oxygen or are under the influence of certain poisons. As the permeability of the capillary walls increases the composition of the lymph changes and the amount of proteins contained in the lymph increases.

Lymph formation may be greatly increased by introduction of certain substances known as *lymphagogues*. These include peptones, extracts from different organs and bile. These substances, apparently, change the permeability of the walls of the capillaries. Lymph formation may also be increased by injection of concentrated solutions of sodium chloride, urea and certain other substances into the blood stream. In this case the concentrated solutions of crystalloids increase the osmotic pressure in the blood and cause water to pass into the latter. Owing to this the total volume of the blood increases and the pressure in the capillaries rises, on the one hand, and the oncotic pressure drops because of a decrease in the concentration of proteins, on the other hand. All this tends to increase the lymph formation. A change in lymph formation in response to stimulation of afferent nerve fibres has been described (data of L. Orbeli's laboratory); Hungarian investigators (Dishvan and associates) recently reported that following the removal of the sympathetic chain the lymphatic system retains less fluid injected into the lymphatic vessels of the extremities.

The rate of the lymph flow in the lymphatic vessels is very low. It is dozens of times as slow as the flow of blood in the veins. Thus, in the main lymphatic vessel in the neck of the horse the rate of the lymph flow was estimated at 270 to 300 mm. per minute.

In the lower vertebrates—fish, Amphibia and reptiles—the lymph flows because of automatic contractions of "lymphatic hearts," distended portions of the lymphatic vessels with thickened muscular walls. In man and in the higher vertebrates as new amounts of lymph are formed, the lymph mechanically forces out that which has until then filled the lymphatic capillaries. In the small lymphatic vessels the pressure of the lymph is 8 to 10 mm. H_2O. In the thoracic duct, where the latter drains into the subclavian vein, the pressure of the lymph is the same as in the large veins, i.e., below atmospheric. A slight difference in pressures conditioned by the lymph flow is thus created. Furthermore, as the skeletal muscles contract, separate places in the lymphatic vessels and in the tissue spaces are compressed and the lymph is squeezed out of them. The valves in the lymphatic vessels prevent the backward flow of the lymph and thus aid in its flow towards the thoracic duct. Finally, the lymph can be moved by peristaltic contractions of the lymphatic vessels themselves.

Despite the slow flow of the interstitial fluid and of the lymph through the thoracic duct, their daily amount flowing through the thoracic duct of the dog equals 1/5 of its body weight (R. Heidenhain).

PART III

CIRCULATION

CHAPTER 9

GENERAL INFORMATION ON CIRCULATION

Discovery of Circulation and the Principal Stages in Its Study

In 1628 William Harvey discovered the functions of the heart and its movements by performing numerous vivisections and observing facts rather than by studying books of various authors. He discovered that a cut in any artery could drain the body of all of its blood which meant that all the blood contained in the body sooner or later flowed through this artery. Harvey observed that by pressing on a vein located close to the skin he made its portion farther away from the heart swell up, hence, the blood flowed to the heart along the veins. Tying an artery off caused its part above to enlarge and distend as though congested; it followed that the blood flowed along the arteries away from the heart. Experimenting on animals Harvey measured the amount of blood pumped by the heart into the aorta per minute and estimated that it constituted dozens of litres per hour which was possible only if the blood driven through the arteries by the heart returned to the latter along the veins. Harvey formulated his inferences as follows: theoretical studies and experiments have confirmed that the blood passes through the lungs into the heart because of the contraction of the ventricles from which it is driven throughout the body; it penetrates into the veins and "tissue pores" and along the veins, at first fine and then larger veins, returns from the periphery to the centre and, finally, through the vena cava reaches the right atrium. The blood, thus, flows in enormous quantities along the arteries from the centre to the periphery and along the veins from the periphery to the centre. This amount of blood is greater than could be produced by the food and larger than is required to nourish the body. It must necessarily be concluded that the blood of animals is in constant circulation.

Harvey did not know of the existence of capillaries which he designated as "tissue pores." Having no microscope he could not see them and the assumption of their existence was a brilliant conjecture based on true premises. The capillaries were discovered by Malpighi in 1661 after Harvey's death.

The next important event in the study of the circulation was the determination of arterial blood pressure (Hales, 1732).

The physiology of circulation began to be developed intensively only in the forties of last century. Since then the processes occurring in the circulatory system have been graphically recorded, the amount of blood in the body has been measured and the problem of the significance of the

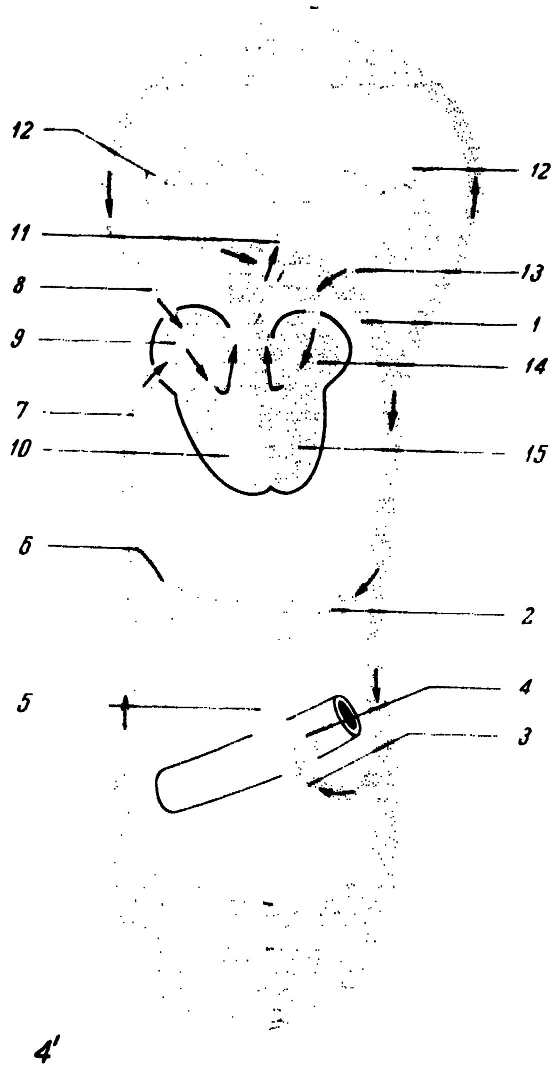


Fig. 11. Diagram of circulation in man.

1 aorta; *2* hepatic artery; *3* one of intestinal arteries; *4* capillary network of systemic circulation; *5* portal vein; *6* hepatic vein; *7* and *8* inferior and superior venae cavae; *9* right atrium; *10* right ventricle; *11* pulmonary artery; *12* capillary network of pulmonary circulation; *13* one of four pulmonary veins; *14* left atrium; *15* left ventricle. Lymphatic vessels are shown in yellow.

various physical factors involved in the movement of the blood has been studied. The study of circulatory regulation began at the same time.

The important study made by Walther in Kiev in 1842 established the existence of nervous influences on the functions of the circulatory system. He demonstrated that excitation of the "sympathetic threads" contained in the sciatic nerve of the frog led to constriction of the blood vessels in its leg. Then discoveries followed one another. It was established that the vagus inhibited the heart (Weber Brothers, 1845) and that the heart rate increased in response to stimulation of the sympathetic nerve fibres (Bezold, Cyon); the influence of different nerves on the vessels was studied in detail (Claude Bernard) and reflex changes in the circulation which regularly occurred in response to stimulation of the afferent fibres running from the receptors of the aorta were discovered (Cyon and Ludwig, 1866). F. Ovsyannikov ascertained that definite portions of the medulla oblongata contained nervous structures whose destruction deranged reflex regulation of the vessels. At about the same time (the sixties of last century) N. Kovalevsky, M. Traube et al., demonstrated that circulation altered in response to an accumulation of carbon dioxide in the blood.

In 1880 to 1890 Pavlov pointed out the ways to study the normal regulation of circulation by his systematic experiments and showed that it could be investigated under conditions of a *chronic* experiment on healthy non-anaesthesized animals. It was in such animals that he found the blood pressure was quite constant and ascertained that the constancy was maintained by a redistribution of the blood regulated by the nervous system.

Clinical studies have always been of essential importance in investigating the circulation. Clinical observation makes it possible to study the circulatory changes produced in man by ailments of the heart, the blood vessels, the nervous system, etc. Clinical needs have led to the development of methods for taking the blood pressure in the human arteries and veins, and for measuring the amount of blood pumped by the heart.

Functions of the Various Divisions of the Circulatory System and the Significance of Circulation

Systemic and pulmonary circulation. In vertebrates circulation takes place in a *closed* system of vessels including the central organ of circulation, i.e., the heart (Fig. 11). In mammals the blood vessels form two circuits—lesser and greater—which communicate with one another through the heart. Along the *greater (systemic) circuit* the blood is driven by the left ventricle and is carried to all the organs of the body except the lungs; after passing through the capillaries of these organs it enters the right atrium by way of the venae cavae. Passing from the right atrium into the right ventricle the blood is driven by contractions of the latter into the *lesser (pulmonary) circuit.* In this circuit the blood flows from the right ventricle through the pulmonary artery and its branches, the pulmonary capillaries, from which it returns to the left atrium along four pulmonary veins. Passing from the left atrium into the left ventricle it is again pumped into the systemic circulation.

The heart is a hollow muscular organ. The longitudinal septum (running from the base of the heart to its apex) divides it into right and left halves, the transverse groove (altrioventricular groove) divides each of these halves into atria and ventricles.

The arteries are vessels along which the blood flows from the heart to the capillaries. Each artery gives off arterial trunks of a lesser diameter which, in their turn, branch out into progressively smaller arteries. The *walls of the arteries, even their minutest branches, the arterioles, are made up of endothelium and layers of muscular and connective tissue, owing to which the substances dissolved in the blood cannot penetrate through the arterial walls into the interstitial spaces.*

The capillaries are minutest vessels connecting the arterial and venous systems. The *exchange of substances between the blood and the tissues* takes place through the capillary walls in the systemic circulation, while the exchange of gases between the blood and the air occurs through the capillary walls in the pulmonary circulation. The number of capillaries is enormous; there is not a single organ in which the distance between the capillaries exceeds a small fraction of a millimetre. The walls of the capillaries are built of only one layer of endothelial cells; they are not thicker than 0.005 mm., so that various substances easily penetrate through them from the blood into the tissues and from the tissues into the blood.

The veins are the vessels along which the blood returns to the heart. From the capillaries of the systemic circulation the blood passes into venules (very small veins) which merge forming larger veins, the latter emptying into veins of a still larger diameter. All of the blood finally collects in two large venous trunks—the superior and inferior venae cavae—which drain into the *right* atrium. In the pulmonary circulation the pulmonary capillaries merge into small veins which finally form four pulmonary veins emptying into the *left* atrium (these are the only veins in the body carrying arterial blood).

Significance of Circulation

Blood circulation ensures the exchange of substances between all the tissues of the body and the external environment and the transport of various substances from one bodily organ to another.

In most multicellular animals oxygen from the external environment and nutritive materials from the intestine cannot reach the tissues directly.

Only the movement of the blood, which carries oxygen and nutritive substances to all tissues, provides for a replenishment of the compounds consumed by the body in the process of metabolism. It is also the blood that ensures excretion of the end products of the body's metabolism (carbon dioxide, ammonia, etc.) whose accumulation in the tissues would lead to an impairment of their functions.

None of the body tissues can function normally without receiving the compounds produced in other tissues and transported from the site of production to other organs again only by the blood. Because of the blood-flow the hormones, each of which is produced only by a certain endocrine gland (see Chapter 39), are carried throughout the body.

Circulation also ensures the liberation of heat by the organs producing large amounts of heat to those producing less (the respiratory organs and the skin). Normal vital activity of the body is possible only if circulation is continuously regulated, which ensures correspondence between the functions of the different organs and the amount of blood flowing through them, as well as the maintenance of a relative constancy in the arterial blood pressure.

The significance of circulation becomes particularly clear when we consider the consequences of its cessation.

Not all organs cease functioning as soon as the blood stops flowing through their vessels. The functions of the most differentiated nervous tissue, the tissue of the cerebral cortex and of the retina of the eye, ceases practically immediately after the cessation of circulation; coma ensues the moment blood stops flowing to the brain; cessation of circulation for more than 5 or 10 minutes leads to necrosis of the higher divisions of the brain. The heart stops almost as soon as the flow of blood through its vessels (coronary) ceases, but irreversible changes develop in it comparatively slowly. The functions of the kidneys and liver discontinue soon after complete anaemization (within 10 to 20 minutes). Paralysis of the skeletal muscles ensues 20 to 30 minutes after the blood stops flowing through the latter, but the changes in the skeletal musculature become irreversible only after 1.5 to 2 hours of total anaemization, and tourniquets can, therefore, be applied to stop haemorrhages from the vessels of the extremities for 1.5 to 2 hours. The smooth muscles and connective tissue can endure cessation of the blood flow for a relatively longer time and not infrequently continue functioning several hours after circulation has stopped.

The disorders of the function and the ensuing necrosis of the tissues after cessation of the blood supply are essentially due to the discontinuance of the oxygen flow to the tissues and the deleterious effect of the insufficiently oxidized metabolites (lactic acid, etc.) accumulating in the tissues during anaerobic metabolism.

Cessation or impairment of the blood supply to any organs cause grave, not infrequently fatal, diseases conditioned by extreme constriction (spasm) of the vessels or their occlusion by a clot of coagulated blood (thrombus). Thus, myocardial infarction, a grave heart ailment, results from a thrombosis of cardiac vessels. Cases of death due to thrombosis of the pulmonary artery have been reported; there are thromboses of the vessels of the brain, the internal organs and the extremities (most frequently the lower). The outcome of the disease in large measure depends on whether *collateral circulation*, i.e., blood supply through a newly formed or considerably developed existing vascular network will be fast enough to provide blood by by-passing the occluded vessels.

Evolution of the Cardiovascular System

The lower invertebrates have neither blood vessels nor blood and the cells of the organism exchange substances with the external environment by a direct penetration of water, oxygen and nutritive materials into the tissue fluid which moves slowly in the intercellular passages.

Phylogenetic development gives rise to increasingly broader avenues for the circulation of tissue fluid, but we can speak of a circulatory system only when special vessels with their own walls have appeared. In invertebrate animals (except the *Annelida*) this system of vessels is not yet closed; the vessels are interrupted by slits, lacunae, which do not have their own walls. A closed circulatory system appears only in the Annelida. Hence, an increasing isolation of the vessels into a closed system is characteristic of the evolution of the circulatory apparatus.

The second characteristic feature in the development of the cardiovascular system is the progressive differentiation of a special muscular organ whose contractions are responsible for the movement of the fluid filling the vessels. Worms, for example, and even the lower *Chordata* (*amphioxus lancellatum*) have no heart as such, but a dorsal vessel whose muscular wall pulsates rhythmically. In the process of evolution the rhythmic contractions of vessels become unimportant and a special muscular organ, the heart, develops.

A division of the heart into an atrium and a ventricle begins to show in fish. The entire blood pumped by the heart is directed in fish towards the gills (Fig. 12, *I*), in whose capillaries it is oxygenated; from the gills the blood goes to blood vessels which in higher animals correspond to the systemic circulation. After passing through the capillaries of all the organs the blood returns to the heart which, thus, receives only venous blood.

The *Amphibia* (Fig. 12, *II*) already have two isolated atria: all of the venous blood collecting from the capillaries of the systemic circulation flows into the right atrium, while the blood returning from the lungs drains into the left atrium. There is only one ventricle, however, so that the arterial and venous blood mix in it. It is the higher reptiles (crocodiles) who, finally, show a four-chamber heart and a fully specialized system of systemic and pulmonary circulation (Fig. 12, *III*).

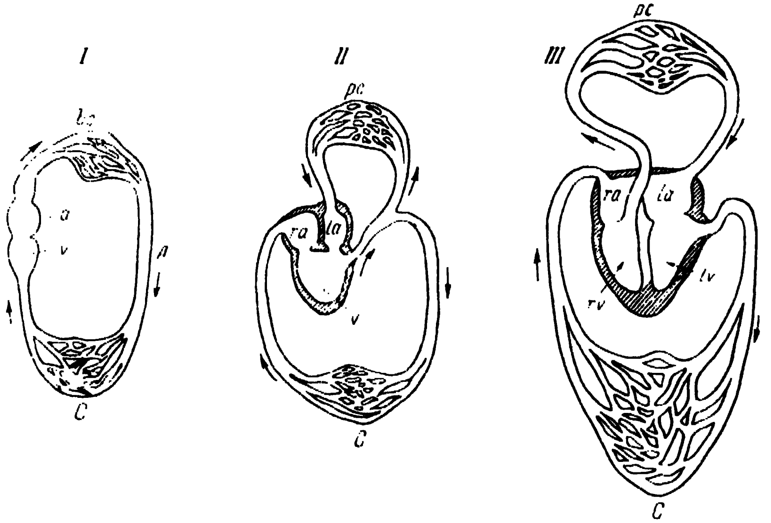


Fig. 12. Diagram showing evolution of structure of blood-vascular system.

I—in fish; *II*—in Amphibia (frog); *III*—in mammals; *V*—ventricle (single); *C*—capillaries of systemic circulation; *A*—atrium (single); *bc*—branchiate capillaries; *pc*—pulmonary capillaries; *la*—left and *ra*—right atria; *rv* and *lv*—right and left ventricles respectively.

Arrows show direction of blood flow.

The evolution of the structure of the circulatory system is accompanied by an evolution of its functions. The flow of the blood is accelerated; the regulation of circulation grows increasingly more complex.

CHAPTER 10

PUMPING FUNCTION OF THE HEART

The Cardiac Cycle. Valves of the Heart

Sequence of the phases of cardiac function. The unceasing flow of the blood along the vessels is conditioned by the activity of the heart. Each contraction of the heart drives the blood from the left ventricle into the aorta and from the right ventricle into the pulmonary artery. During the relaxation of the ventricles the latter are filled with blood which enters the left atrium from four pulmonary veins and the right atrium from the superior and inferior venae cavae. The period of a single contraction with the ensuing relaxation of the heart is referred to as a *cardiac cycle.* The contraction of the heart muscle is called a *systole* and its relaxation a *diastole.*

Each cycle in the activity of the heart begins with a systole of the atria which is followed by their diastole. The systole of the ventricles begins immediately after the end of the systole of the atria. The systole of the ventricles is followed by their diastole during which both the atria and the ventricles are relaxed. This is a pause of the whole heart.

Role of the valves of the heart. Because of the valves the contractions of the heart drive the blood only in one direction: from the atria into the ventricles and from the ventricles into the arteries.

The atrioventricular valves are located in the apertures between the atria and the ventricles (the bicuspid or mitral in the left and the tricuspid in the right apertures).

During diastole of the whole heart and during systole of the atria the leaflets of the atrioventricular valves hang down into the cavities of the ventricles without, however, touching their walls (Fig. 13, *A*). At this time the blood flowing from the veins to the heart freely passes through the atria into the ventricles.

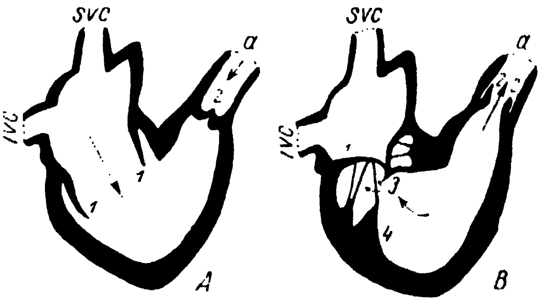


Fig. 13. Diagram showing action of heart valves Left position of valves during atrial systole and during diastole of whole heart (after end of ventricular relaxation) at this time atrioventricular valves (1) are open and semilunar (2) are shut. Right — position during ventricular systole (after period of tension); atrioventricular valves are shut semilunars are open; 3 — chordae tendineae; 4 — papillary muscles. SVC and IVC — superior and inferior venae cavae respectively.

With the beginning of the ventricular systole the muscles of the ventricles tense and forcefully press on the blood contained in the ventricular cavities. The pressure on the sides of the valvular cusps facing the walls of the ventricles exceeds that exerted on them by the atria. This presses the leaflets of the atrioventricular valves to each other and they assume the position shown in Fig. 13, *B*. The higher the pressure in the ventricles the greater the force that shuts the atrioventricular valves.

The closing of the atrioventricular valves is prepared already by the end of the systole of the atria because by this time the reverse wave of the blood driven out of the atria and reflected from the walls of the ventricles reaches the sides of the leaflets facing the ventricular cavities. This forces the leaflets of the atrioventricular valves somewhat closer to each other by the end of the atrial systole, while the rise in ventricular pressure closes the valves, making their leaflets adhere closely to each other the moment the ventricular systole begins.

The chordae tendineae, i.e., tendinous cords attached to the valvular borders and to the papillary muscles of the ventricles, play an essential part in the action of the atrioventricular valves. By contracting the papillary muscles stretch these tendinous cords owing to which the edges of the valves slightly fold towards the ventricles and their leaflets hug each other for some distance rather than just touch margins. Besides, the pull of the tendinous cords does not allow the leaflets of the valves to bend back into the atrial cavities under the strong pressure of the ventricular blood.

A certain role in closing the atrioventricular openings is apparently played by the circular muscles which line them. During ventricular systole the atrioventricular openings become constricted, which may also prevent the blood from flowing back into the atria.

If the atrioventricular valves do not shut tight the blood during contraction of the ventricles is driven not only into the arteries, but also back into the atria. This condition is called insufficiency of the corresponding atrioventricular valve; it may result not only from a destruction of the leaflets of the valves, but also from an impairment of the papillary muscles, the tendinous cords and the muscles surrounding the atrioventricular opening.

The atrioventricular valves are closed when the pressure in the ventricles is higher than in the atria; hence, they are closed throughout the systole of the ventricles and are open during the diastole of the whole heart and during the systole of the atria.

The semilunar valves are located where the blood passes from the left ventricle into the aorta and from the right ventricle into the pulmonary artery. In structure these valves resemble three pockets whose edges are directed towards the aorta or the pulmonary artery. The space between the walls of these vessels and the inner surface of the valves is filled with blood. When the pressure in the aorta or in the pulmonary artery rises above that in the ventricles the blood straightens out the edges of the semilunar valves and presses them to each other (Fig. 13, *B*). The more the pressure in the aorta and in the pulmonary artery exceeds that in the ventricles the closer the edges of the semilunar valves are pressed to each other.

The semilunar valves are closed when the pressure in the aorta (and in the pulmonary artery) is higher than the pressure in the ventricles; hence, they are closed throughout the diastole of the heart and are open only during the systole of the ventricles when blood is being driven out of them.

Phases of Cardiac Activity

The heart imparts motion to the blood because each contraction (systole) of its ventricles forcefully drives the blood into the arteries. The blood filling the heart experiences a pressure exerted on it by the walls of the heart which tense during systole. As a result of this pressure the blood is forced in the direction which offers no obstacles to its flow, i.e., in the direction in which the valves open.

To understand the work of the heart we must observe the changes in pressure in its cavities (and in the aorta) during the entire cycle of cardiac activity.

Recording the pressure in the cavities of the heart. A mercury manometer cannot be used because owing to the mass and, consequently, the high inertia of mercury, the oscillations of the mercury column are not fast enough to follow the rapid variations in the blood pressure in the cavities of the heart. For this reason use is made of a membrane manometer (with a minimum of inertia) in which the variations of pressure cause displacements of the thin elastic rubber membrane stretched over a small hollow capsule (Fig. 45). The capsule communicates by means of a liquid-filled tube with the organ in which the variations in pressure are being recorded. A small mirror is glued to the rubber membrane of the manometer; the shaft of light reflected by the mirror is directed at a slit behind which sensitized paper moves.

To record the pressure in the cardiac cavities without opening the thoracic cavity Marey proposed that a so-called *cardiographic probe*, i.e., a hollow tube, be inserted into the right half of the heart through the jugular vein. A small rubber inflatable balloon is attached to the end of the probe which is being inserted into the heart; the balloon communicates with the manometer through the tube of the probe. The manometer thus records all the variations in pressure occurring in the balloon inserted into the heart. A probe consisting of two tubes may also be used; in this case the balloons attached to each tube are inserted—one into the atrium and the other into the ventricle (Fig. 14). The cardiographic probe is frequently inserted directly into the heart cavity through an incision in its wall.

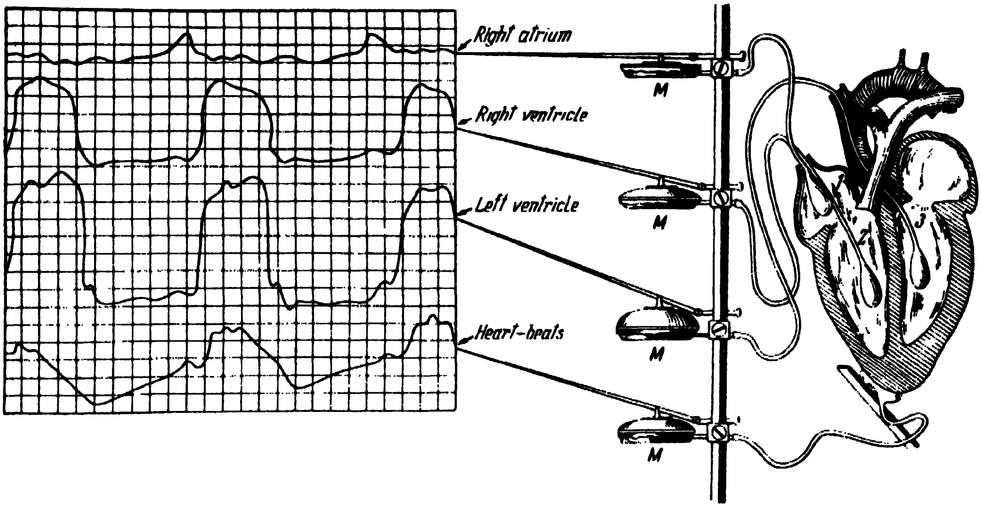


Fig. 14. Recording pressure in cardiac cavities (experiment by Chauveau and Marey) by cardiographic sounds and pneumatic transmission.

Balloons on the cardiographic sounds are inserted through jugular vein into right atrium *(1)* and right ventricle *(2)*, and through carotid artery into left ventricle *(3)*. Balloons are filled with air and are connected with Marey's recording capsules *(M)*. Oscillations of pointer corresponding to every change in pressure in cardiac cavities are recorded on kymograph. Movements of apex of heart (heart-beats) are simultaneously recorded through Marey's capsule.

These methods have made it possible accurately to record the variations in pressure in the cardiac cavities of the higher animals (dogs, horses) and in some operations also in the heart of man.

Systole of the atria. The cardiac cycle begins with the systole of the atria. The pressure in the cavities of the atria rises during their systole (by 2 to 5 mm. Hg).

There are no valves between the atria and the veins, but during the systole of the atria the circular muscles surrounding the veins at the points of their entrance into the atria contract. Owing to this only a negligible amount of blood flows from the atria back into the veins.

The systole of the atria is followed by their diastole which lasts till the beginning of the atrial systole of the next cardiac cycle.

Systole of the ventricles. The systole of the ventricles begins immediately after the end of the atrial systole. Both ventricles contract simultaneously and the sequence of events is the same for both.

Period of tension. Contraction of the ventricular muscles produces a sharp rise in the pressure of the blood contained in the ventricles. The pressure in the ventricles immediately rises above that of the atria and the atrioventricular valves, therefore, close in the very beginning of the ventricular systole. The semilunar valves open somewhat later because by the end of the diastole of the left ventricle the pressure in the aorta usually still equals 50 to 70 mm. Hg. (p. 136) and the semilunar valves cannot open as long as the pressure in the ventricle is below that in the aorta. It takes a little time for the pressure in the contracting ventricles to rise above the pressure in the aorta and in the pulmonary artery. Hence, there is a brief interval in the very beginning of the ventricular systole when the atrioventricular valves are *already* closed and the semilunars have not *yet* opened. At this time the ventricular cavities are closed.

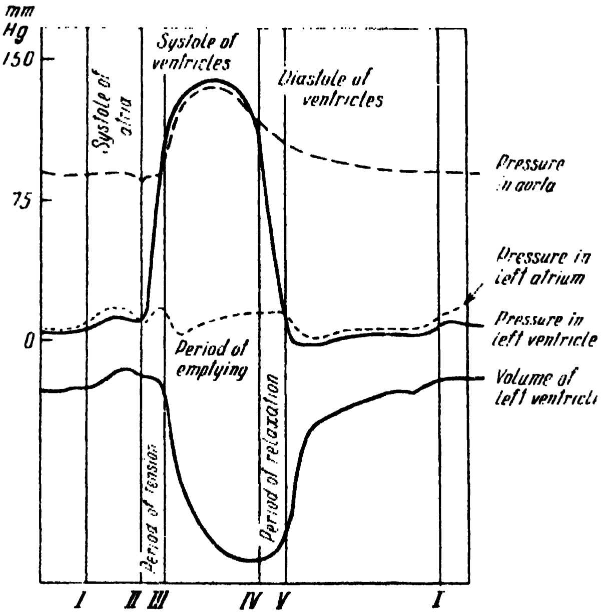


Fig. 15. Recording changes in volume of left ventricle and variations in pressure in left atrium. left ventricle and aorta during cardiac cycle.

I - beginning of atrial systole; *II* beginning of ventricular systole and moment of closing of atrioventricular valves; *III* moment of opening of semilunar valves; *IV*— end of ventricular systole and moment of closing of semilunar valves; *V* - opening of atrioventricular valves. Descent of line showing volume of ventricles corresponds to their emptying (decrease in volume).

Since liquids are practically incompressible the muscle fibres of the ventricles cannot shorten before the semilunar valves open and the contraction of the ventricular muscles is expressed only in its increased tension.* The short phase in the beginning of the ventricular systole (about 0.05 sec.) when their cavities are closed is, therefore, called the *phase* or *period of tension*. By tensing and not shortening the ventricular muscles exert during this period an increasingly higher pressure on the enclosed blood. Fig. 15 demonstrates the period of tension by the fact that between verticals II and III, the former corresponding to the moment the atrioventricular valve closes and the latter to the moment the aortic valve opens, the volume of the ventricles (lower line in the figure) and the pressure in the aorta undergo practically no change, whereas the pressure in the ventricle (upper solid line) rises sharply.

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* When stimulated muscle fibres do not shorten, but only tense, their contraction is called isometric. The period of tension is, therefore, sometimes designated as the isometric period.

Period of ejection. The moment the pressure developed by the muscles of the ventricles exceeds that in the aorta the aortic valves open and the period of ejection begins; this period lasts about 0.25 sec. Fig. 15 shows that the line indicating the pressure in the ventricular cavities crosses the line indicating the pressure in the aorta and runs above it throughout the period the blood is being forced out of the heart.

In the beginning of this period the pressure in the ventricular cavities rapidly rises, reaching 130 to 150 mm. Hg. At this time the blood quickly flows from the left ventricle into the aorta and from the right ventricle into the pulmonary artery; the volume of the ventricles sharply decreases. This is the period of *maximal* ejection.

About 0.05 to 0.1 sec. after the opening of the semilunar valves the flow of blood from the heart begins to slow down and the contraction of the ventricular muscles weakens. The pressure in the left ventricle is still higher than in the aorta, its muscles are still contracting, but the pressure both in the ventricle and in the aorta is beginning to fall. This period is referred to as the period of *reduced ejection.*

Period of relaxation. Approximately 0.25 to 0.3 sec. after the opening of the aortic valve the systole of the ventricles ceases and the diastole begins. Immediately after the beginning of the ventricular diastole the aortic valve closes because the moment the muscles of the ventricles start relaxing the pressure in the ventricular cavities at once sharply falls below that in the aorta (Fig. 15, *IV*). Now again (this time against the background of developing relaxation) a short period ensues (approximately 0.08 sec.) when the aortic valve is already closed and the atrioventricular valves are not yet open. During this time pressure in the ventricular cavities drops from the level of the pressure in the aorta to that in the atrium. When the pressure in the ventricles falls slightly below that in the atria the atrioventricular valves open (Fig . 15, *V*) and the *diastole of the whole heart* ensues lasting till the beginning of the next atrial systole.

The phenomena in the right half of the heart (right atrium and right ventricle) are a reduced replica of those observed in the left half of the heart. The moments when the valves open and close coincide. The period of tension and the period of ejection occur simultaneously and the curve showing the pressure changes through the cardiac cycle in the right atrium, the right ventricle and in the pulmonary artery repeats the curves (Fig. 15) illustrating these relations for the analogous divisions of the left half of the heart and the aorta. The only difference is that the pressure change in the right ventricle is less than the corresponding changes in the left ventricle and in the aorta. By the end of the diastole the pressure in the aorta equals 60 to 80 mm. Hg, while in the pulmonary artery it is only 8 to 15 mm. while the blood is being rapidly forced out of the heart the pressure in the aorta rises to 130 to 150 mm. Hg, while in the pulmonary artery it reaches only 15 to 30 mm. (in the cavities of the right and left atria the changes in pressure during the cardiac cycle are almost the same).

Cardiac diastole and filling of cardiac cavities with blood. The blood can flow from the veins into the atria throughout the systole of the ventricles from which the atria are at this time separated by the atrioventricular valves. The systole of the ventricles even fosters the passage of blood from the veins into the atria because at the time the blood is being driven out of the heart the septum between the ventricles and the atria is pulled towards the apex of the heart which leads dilatation of the atrial cavities.

As the atrioventricular valves open the blood accumulated in the atria flows into the ventricles and their volume begins to increase rapidly (see lower line in Fig. 15). Towards the end of the diastole the blood entering the atria from the veins flows from the atria into the ventricles. The end of the ventricular diastole coincides with the atrial systole of the next cardiac cycle.

Duration of the various phases of the cardiac cycle. With 75 heart-beats per minute each cardiac cycle lasts 60 : 75, i.e., 0.8 sec. with the systole of

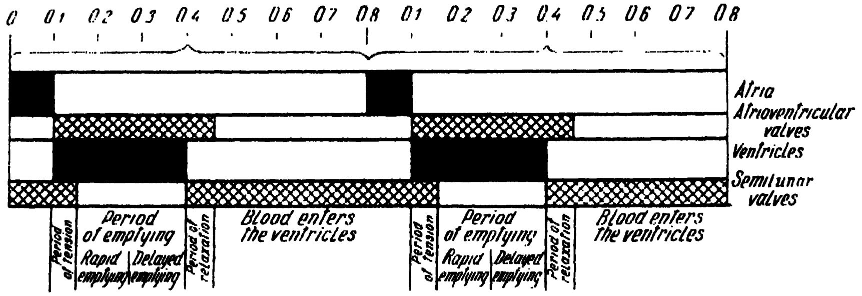

Fig. 16. Time relationship of various phases in cardiac cycle.
Blackened spaces show period of atrial and ventricular systoles respectively; shading represents periods the atrioventricular and semilunar valves are closed. Two cardiac cycles each of 0.8 sec. duration are shown.

the atria lasting about 0.1 sec. and their diastole—0.7 sec. The systole of the ventricles lasts about 0.3 sec., their diastole—0.5 sec. The diastole of the whole heart (atria and ventricles, both) then lasts 0.4 sec. (Fig. 16). These figures are, of course, only of a relative significance; their value depends mainly on the heart rate. With an increase in the heart rate the systole shortens less than the whole cardiac cycle so that the latter shortens mainly at the expense of the diastolic period. For example, with 120 contractions of the heart per minute, when each cardiac cycle lasts 0.5 sec., the ventricular systole still lasts about 0.2 sec., while the ventricular diastole shortens approximately to 0.3 sec.

Arterial and Venous Pulse

The systole and diastole of the heart are inseparably connected with the rhythmic pressure variations in the large arteries and the large veins located close to the heart—pulse waves. These waves must, therefore, be considered in their direct connection with the activity of the heart.

Arterial pulse. In the narrow sense of the word "pulse" means a certain wave of distension which passes over the arterial walls with each contraction of the heart. These waves are easily palpated on the superficial arteries. It has been a practice of long standing to palpate the peripheral pulse in the region of the lower fourth of the forearm because the radial artery passes here directly under the skin and the fascia and lies on a flat bone. Palpation of the radial pulse gives a certain idea not only of the heart (rhythm, force of cardiac contractions), but also of the state of the arterial walls (degree of tension, rigidity, sinuosity, etc.). It enables the clinicist to form a more accurate judgment of the nature of pathological changes in the peripheral arteries.

The pulse waves of the arterial walls pass from the beginning of the aorta over the arterial system with each systole. These waves vary in intensity with the degree of arterial elasticity.

The speed at which the pulse waves of the arterial walls travel is equivalent to that at which the variations in blood pressure are reflected in the arterial stream. This speed is much higher (about 5 to 10 times as high) than the velocity of the blood flow along the arteries. The pulse waves of the arterial walls, therefore, arise in all arteries (except the aorta at the point where it leaves the heart) sooner than the portion of blood driven out of the heart during a given systole reaches the corresponding point. As the elasticity of the arterial walls decreases (for example, in elderly people) and the blood pressure rises the pulse waves travel at a higher speed while the amplitude of these waves (everything else being equal) diminishes. The easily palpated pulse waves of the arterial walls can be recorded by a special instrument called a sphygmograph (Fig. 17).

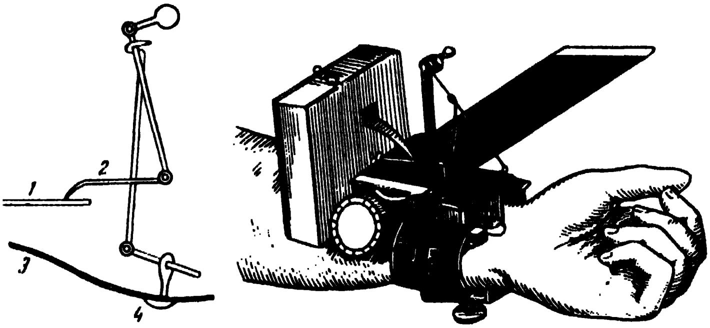

Fig. 17. Sphygmograph and diagram of its construction.

1—stud slightly pressed by spring *(3)* to site where the waves of the radial artery are palpated best; the waves perceived by the stud are transmitted by levers to pointer *(2)* whose movements are recorded on smoked paper *(1)* moved by clock. The degree of pressure of the stud can be regulated.

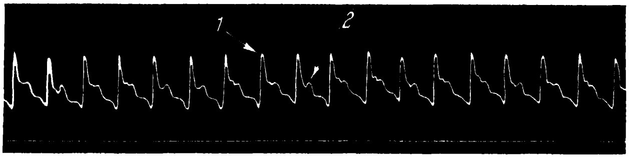

Fig. 18. Normal sphygmogram.

1—main wave; 2—dicrotic wave.

The curve of a pulse record (sphygmogram) always shows (Fig. 18) an ascending limb—anacrotism and a descending limb—catacrotism with secondary waves, the highest of which is referred to as a dicrotic rise or notch. The anacrotism is due to a rise in the arterial pressure during systole, while the catacrotism results from a gradual drop in pressure during diastole. The dicrotic rise is caused by the blood pulsating against the closing leaflets of the semilunar valves at the end of the systole. The blood pulsating against the closing valves produces a wave reflected from the closed valves towards the periphery. A reflected beat arises leading to a very brief increase in the aortic pressure and, consequently, to a corresponding wave in the aortic walls. Thus, the dicrotic wave arises at the same point as the primary wave and travels along the arterial walls at the same speed.

Sometimes the dicrotic rise is so high that it can be mistaken for a cardiac wave (the question is easily settled by comparing the pulse rate with the heart rate counted by the heart-beat). Such pulse is called dicrotic. It is usually due to a low tension in the arterial walls.

The pulse waves (like the pressure variations) travel along the arteries at a definite speed (6 to 12 m/sec.); the less elastic the artery the higher the speed (one can get a visual idea of this by watching the oscillations of a taut or slack cord). The pulse wave travels the distance to the radial artery (about 80 cm.) in 0.04 to 0.08 sec.

Some peculiarities of the pulse can be determined even by simple palpation. If the pulse waves disappear when the artery is slightly compressed, the pulse is referred to as an easily compressible or soft pulse (*pulsus mollis*) most frequently encountered in fevers.

The opposite condition of the pulse (*pulsus durus*) is characteristic of high tension of the arterial walls. This pulse variety is most frequently observed in chronic nephritis and in lead colic with a sharp rise in the vascular spasticity typical of these ailments.

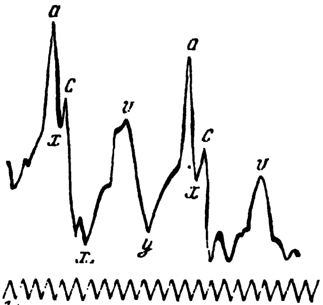

Fig. 19. Venous pulse curve—phlebogram (after L. Fogelson).

Depending on the speed at which the pulse wave develops we speak of a *fast* pulse (*pulsus celer*) and a *slow* pulse (*pulsus tardus*). The former is a symptom of insufficiency of the semilunar valves of the aorta, the latter is characteristic of the unyielding vascular walls in atherosclerosis.

An irregular pulse revealed by comparative palpation of both radial arteries denotes aortic aneurism.

Venous pulse. In the veins located close to the heart it is possible to detect variations in pressure connected with the activity of the heart and producing waves in the venous walls. These waves are designated as the venous pulse.

To record the venous pulse a hollow needle inserted through a puncture in the skin into a vein located close to the heart (usually the jugular vein) is connected with a manometer or a capsule, which registers the variations in pressure that are communicated to Marey's recording capsule, fastened over the vein.

The curve of the venous pulse—phlebogram—shows (Fig. 19) *three* waves corresponding to a rise in the venous pressure (*a*, *c* and *v*). Wave *a* is produced by the systole of the right atrium. During the tension in the right ventricle the rise in pressure in its closed cavity is transmitted through the closed leaflets of the atrioventricular valve to the blood which fills the right atrium and the near-by veins and gives rise to wave *c*. The third wave (*v*) is observed during the second half of the ventricular systole and is due to the inflow of blood from the veins into the atria. The sharp drop of the curve from *c* to x_1 corresponds to the fall in the atrial pressure at the time the blood begins to be driven out of the ventricles.

The curve of the venous pulse thus shows the variations in blood pressure in the large veins resulting from the atrial systole, the period of tension of the ventricular systole, the blood being driven out of the ventricle and the passage of blood from the atrium into the ventricle after the opening of the tricuspid valve (drop in pressure from v to y).

CHAPTER 11

PHYSICAL PHENOMENA CONNECTED WITH CARDIAC ACTIVITY. CARDIAC SOUNDS

Nature of cardiac sounds and their recording. Two separate sounds are auscultated in each normal cardiac cycle. These sounds are known as *cardiac sounds.* We can easily verify the fact that two sounds really correspond to each cardiac cycle if we simultaneously count the cardiac sounds and the pulse waves of the arterial wall; normally there are always twice as many cardiac sounds as there are pulse waves.

First we hear a longer sound of a low tone; this is the so-called *first cardiac sound.* After a brief pause it is followed by a higher-pitched but shorter sound, the *second sound.* After this comes a longer pause than the one between the two sounds. With a new cardiac cycle the two-tact rhythm of cardiac sounds is repeated (Fig. 20).

The cardiac sounds can be heard by pressing the ear to the thorax, but it is more convenient to use a phonendoscope. A phonendoscope is a receiving capsule equipped with a membrane which magnifies the sound waves transmitted from the capsule of the phonendoscope along rubber tubes whose ends are inserted into the ears.

To record the cardiac sounds the sound waves are usually transformed into electric waves. The electric waves rising with each sound wave are detected by a galvanometer or an oscillograph. They can be recorded by projecting onto a moving photo-film the oscillations of a beam of light reflected by a mirror of the galvanometer (Fig. 21).

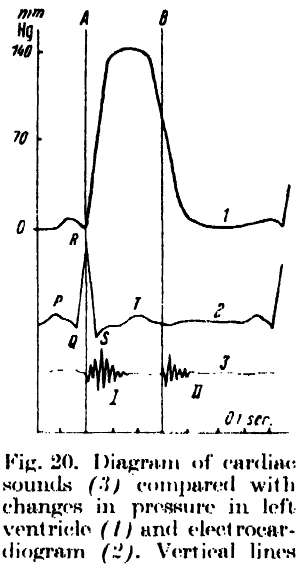

Fig. 20. Diagram of cardiac sounds *(3)* compared with changes in pressure in left ventricle *(1)* and electrocardiogram *(2)*. Vertical lines *A* and *B* represent beginning and end of ventricular systole. Roman figures show first and second cardiac sounds.

Causes of cardiac sounds. By simultaneously recording the pressure in the ventricular cavity and the cardiac sounds (Figs. 20 and 21) we see that the first sound arises in the beginning of the ventricular systole and lasts approximately 0.12 sec. (throughout the period of tension and the beginning of the period when the blood is forced out of the heart). This sound is called the *systolic sound.*

The second sound is produced at the moment the semilunar valves close and lasts about 0.08 sec. This sound is referred to as the *diastolic sound.*

Several factors are responsible for the first cardiac sound. The initial part of the first sound is conditioned by sound phenomena connected with the systole of the atria. A certain part in this is played by the vibration of the atrioventricular valves and the *chordae tendineae* which is due to a sharp rise in ventricular pressure. But the contraction of the ventricular muscles is the most significant in producing the first sound since in special experiments on animals it was possible to hear the first sound (though weakened) even after the atrioventricular valves had been destroyed. There are reasons to believe that the sharper the pressure rises in the ventricles during systole the stronger is the first cardiac sound, everything else being equal.

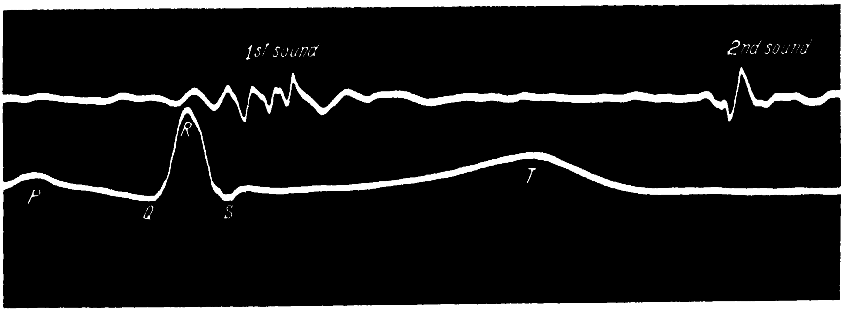

Fig. 21. Record of cardiac sounds (top) and electrocardiogram (bottom). Atrial component of first sound is visible. Record was made by instruments of the Institute of Therapy of the U.S.S.R. Academy of Medical Science (after I. Savchenkov).

The second heart sound is produced by the closing of the semilunar valves and the vibration of their elastic walls. The higher the pressure in the aorta (and correspondingly in the pulmonary artery) the stronger the sound.

Investigation of the cardiac sounds is of enormous practical importance since a number of disorders of the cardiac function leads to changes in these sound phenomena.

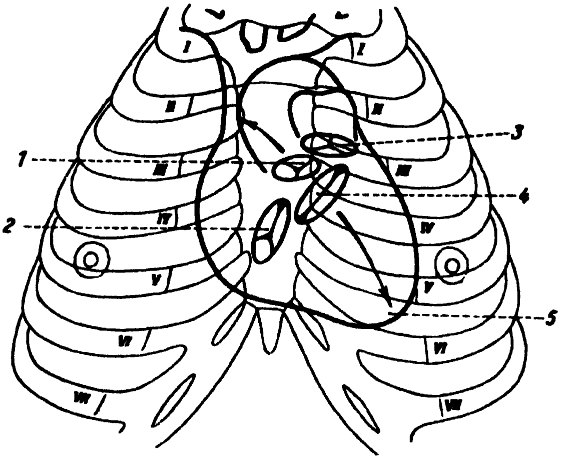

Fig. 22. Position of heart in thoracic cavity and auscultation areas.

1—Projection of aortic valve; *2*—Projection of and auscultation area of tricuspid valve; *3*—Projection of and auscultation area of valves of pulmonary artery; *4*—Projection of mitral valve; *5*—apex of heart. Upper arrow shows auscultation area of aortic valve, lower arrow—bicuspid (mitral) valve.

If, for example, the function of the mitral valve is impaired, the blood during the systole of the ventricles passes not only into the aorta, but also back into the left atrium. During the systole the ventricle is not fully closed and the pressure in its cavity rises less sharply than normal; the vibration of the mitral valve and the *chordae tendineae* is weaker, the first sound is, therefore, less sonorous and the flow of the blood from the ventricle into the atrium leads to the production of an adventitious sound during the entire systole—the ***systolic murmur.*** If the aortic valve does not fully close the blood passes from the aorta back into the ventricle during ventricular diastole resulting in a ***diastolic murmur.***

Separate auscultation of the cardiac sounds. The first cardiac sound is produced in the region of the atrioventricular valves and the second in that of the semilunar valves. Spreading from the point of origin the sound waves are not equally muffled by the different organs and tissues of the thoracic cavity. By auscultating the cardiac sounds at different portions of the anterior surface of the chest wall it is, therefore, possible to detect separately the sound phenomena connected with the function of each of the four valves.

It has been found empirically that the second sound auscultated in the second intercostal space to the right of the sternum is connected mainly with the closing of the aortic valves, while the second sound auscultated in the same intercostal space but to the left of the sternum in large measure reflects the closing of the valves of the pulmonary artery. The first sound determined by auscultating near the sternum between the points of attachment of the fourth and fifth ribs is conditioned mainly by the sound phenomena arising during the activity of the right ventricle and the tricuspid valve (Fig. 22).

Heart-beat, Cardiogram and Size of the Heart

During the contraction of the ventricles the heart changes its position in the thoracic cavity: its base drops and the large vessels stretch. The heart that was flabby during diastole becomes compact, almost hard, during systole. During systole the apex of the heart barely changes its position, but the whole heart rotates somewhat from left to right and the left ventricle is pressed closer to the thoracic wall. This manifests itself on the surface of the thorax in the form of a heart-beat palpated (in slender people visible externally) in the left fifth intercostal space inside the line drawn through the middle of the clavicle.

The record of the heart-beat is called a *cardiogram.*

This record is easily obtained by tying to the chest a rubber-covered capsule with a convex ivory stud glued to it. The capsule is put on so as to have the ivory stud right over the region of the heart-beat. At each beat the stud is pressed in and compresses the air in the capsule. The latter is connected by a tube with another, recording capsule. The rise in pressure in the capsule placed on the chest leads to a rise in pressure in the recording capsule; the rubber that invests it rises and the movements of the pointer are recorded on a moving smoked paper. The record of the cardiogram is of no great practical importance.

The size of the heart is very easily determined by percussion since the sound produced by percussing a finger placed on the chest is duller over the heart than over the air-filled lungs. The most accurate method of determining the size of the heart is photographing its shadow by X-rays to which the heart is less permeable than the lungs.

The size of the heart varies, firstly, with the distension of its cavities by blood and, secondly, with the thickness of the muscles of its walls. The heart normally weighs 250 to 350 gr. (0.4 to 0.5 per cent of the body weight). The distension of the heart resulting from a sustained high arterial pressure and from heart diseases leads to hypertrophy, i.e., to an increase in the mass of its muscle. This is due chiefly to the thickening of each muscle fibre rather than to a growth of new muscle fibres.

Electrocardiography

Action currents in the heart and their recording. As before stated (p. 33), each excited portion of tissue is electronegative in relation to the portion at rest. By connecting two areas of tissue to a galvanometer we, therefore, discover a difference in potentials (action current or potential) at the moment the excitation spreading over the given tissue reaches the point where one electrode is placed, but has not yet reached the point of contact of the second electrode. When the excitation has spread over the whole organ and all its portions are, therefore, in the same state, there is no difference in potential between the two points of the tissue as there is no difference when these areas are in a state of rest.

A. Samoilov

Electric potentials arise in the heart muscle during its activity. The lines of force of the electric field spread in every direction from the point of origin of the difference in potentials. The heart is not symmetrically located in the thoracic cavity and the electric potentials originating anywhere in the organ spread over the body as is shown in Fig. 23. By connecting two points of the body, which are asymmetrical in relation to the electrical axis of the heart, with a sufficiently sensitive and inertia-free recording instrument we can record the electric phenomena of the heart.

The study of the electric phenomena originating during the activity of the human heart has become practically possible since W. Einthoven (1903) used for this purpose a string galvanometer, an instrument which permits of recording not only very weak (with a tension measured in millivolts) but also very rapid electric currents (in this instrument a very fine filament fixed in the field of a strong electromagnet is deflected when an electric current passes through it; magnified by a system of lenses the deflection of the string is photographed on a film moved by the rotating kymograph drum). At the present time more mobile oscillographs, rather than a string galvanometer, are made use of; the recorded current fed to the variously designed oscillographs is considerably amplified by cathode valves. The instruments specially adapted to recording the bio-currents of the heart are called (irrespective of type) *electrocardiographs.*

In recording the electric potentials of the human heart clinically the currents are directed to the electrocardiograph from the following parts of the body (Fig. 24): from the right and left arms (first lead), from the right arm and the left leg (second lead) and from the left arm and the left leg (third lead). The chest leads are frequently used for this purpose; in this case one of the electrodes is placed somewhere on the chest and the second is usually applied to an arm (preferably the right arm). Oesophageal leads are now successfully used: one of the electrodes is inserted into the oesophagus (at various levels) which makes it possible more accurately to isolate the atrial components of the electrocardiogram (see below), since the electrode is then located most closely to the left atrium (if inserted deeper the electrode is close to the wall of the left ventricle). A comparison of the *electrocardiograms* (records of electric phenomena in the heart) taken with different leads makes it possible to reveal the deviations in the position of the heart in the thoracic cavity and to determine the part of the heart in which alterations responsible for the changes in the electrocardiogram (this question is treated in greater detail in courses of diagnosis and in the study of the pathology of circulation) have occurred. The study of electrocardiograms has become a very important method of diagnosing the disorders of cardiac function.

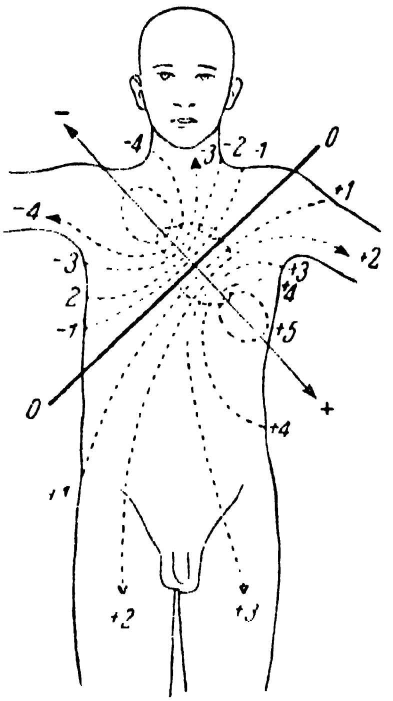

Fig. 23. Spread of lines of current, arising during cardiac activity, through body.

Electric potential conditioned by bio currents of heart is same all along each dotted line, and no difference in potentials is, therefore, detected between any two points lying on same dotted line. By connecting points of body surface with different potentials to electrocardiograph variations in these potentials conditioned by cardiac activity are recorded.

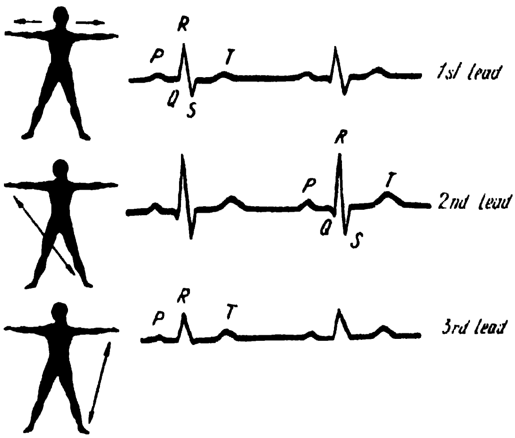

Fig. 24. Standard leads used in electrocardiographic examination.

Arrows point at extremities connected by wires to poles of electrocardiograph: first lead (top), second lead (middle), third lead (bottom). An electrocardiogram of each of these leads is shown on the right (after A. Myasnikov).

Interpreting an Electrocardiogram. Fig. 25 shows an electrocardiogram of a healthy person (second lead). In the cardiogram three rather large waves pointing upward from the middle line and two usually smaller waves pointing downward correspond to each normal cardiac cycle. It is customary to designate these waves from left to right by *P*, *Q*, *R*, *S* and *T* with the *P*, *R* and *T* (in the first and second lead) marking the large waves pointing upward, and the *Q* and *S* marking the small waves (sometimes they are absent) pointing downward, i.e., in the direction opposite to wave *R*.

Wave *P* is due to the *excitation of the atria*. The current resulting from the excitation of the atria always precedes (0.01 to 0.02 sec.) the beginning of the contraction of their muscles. Wave P is the algebraic sum the potentials originating in the right and left atria. If we experimentally cause the left atrium to contract before the right atrium the crest of wave P will not point upward but downward (L. Fogelson); the usually observed upward direction of wave P is due to the fact that the oscillation of the current conditioned by the activity of the right atrium prevails over that depending

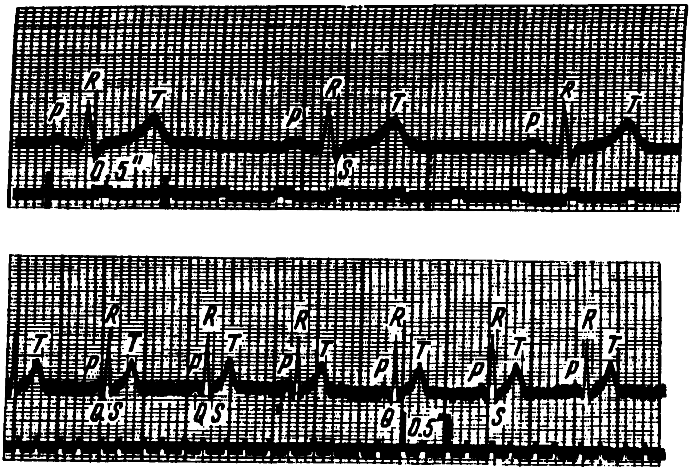

Fig. 25. Electrocardiograms of two healthy people recorded at different speeds.

on the excitation of the left atrium. In oesophageal leads the negative (pointing downward) component of wave P is always present. It has also been established that in the electric potentials, which are due to the activity of the atria (if they are not disguised by superimposed potentials of the ventricular complex), it is possible to detect the same oscillations which are so sharply pronounced in the ventricular complex of the electrocardiogram (see below). In particular, in the atrial part of the electrocardiogram (in the oesophageal lead or in rare ventricular systoles) we see the wave connected with the end of the atrial systole analogous to wave T of the ventricular complex.

Waves Q, R, S and T in the electrocardiogram are due to the rise and spread of the excitation over the muscles of the ventricles and are called the *ventricular complex.* Correspondingly the interval between the origin of waves P and Q (usually 0.09 to 0.12 sec.) is a precise index of the time that passes between the beginning of excitation of the atria and the ventricles.

Wave Q of the ventricular complex of the cardiogram precedes the beginning of the ventricular contraction by about 0.02 sec. The difference in potentials which produces this wave already disappears by the time the atrioventricular valves close. Waves Q, R and S are, no doubt, due to the fact that not all of the ventricular muscles are excited at the same time. Wave Q possibly corresponds to the beginning of excitation in the papillary muscles, wave R—to the excitation of the base of the ventricles and wave S—to the excitation of the apex of the heart.

The absence of current in the interval between waves S and T is explained by the fact that at this period the excitation has already spread over the entire muscular mass of the ventricles and, therefore, there can be no difference in potentials between any two of its points. The nature of wave T is not quite clear as yet. This wave appears at the end of ventricular systole. It is possible that wave T is an electric manifestation of the chemical reduction processes which take place in the ventricular muscles after their excitation ceases. A diminution of wave T (and especially its depression) testifies to pathological disorders of the cardiac function.

An analysis of an electrocardiogram taken with different leads makes it possible, as V. Zelenin was the first to show, separately to judge about the processes of excitation in the left and the right ventricles. It has been found that a normal ventricular electrocardiogram is a result of the interaction of the bio-currents which originate in the right and the left ventricles and run in opposite directions. In hypertrophy of the left ventricle the largest wave of the ventricular complex in the electrocardiogram taken with the third lead (left arm and left leg) points downward, while in hypertrophy of the right ventricle (same lead) it points upward.

CHAPTER 12

ORIGIN AND PROPAGATION OF EXCITATION IN THE HEART. FORCE OF CARDIAC CONTRACTIONS

Contraction of an Isolated Heart

The heart is capable of contracting rhythmically for some time even after it has been removed from the body. Hence, the contractions of the heart muscle may be conditioned by processes occurring in the heart itself.

If no special precautions are taken to safeguard the vital activity of the isolated heart the latter soon ceases to contract and dies because of an accumulation of products of intermediate metabolism which disturbs the enzyme systems and impairs the very fine structure of cardiac tissue. If a fluid, which carries away the products of metabolism formed in the heart, is perfused through the vessels of the isolated heart the vital activity of the isolated organ can be retained for a long time. The composition of the fluid, however, must approximate that of the blood plasma. Ringer's, Locke's or Thyrode's solutions are used for the hearts of the homoiotherms and Ringer's solution for the hearts of the poikilotherms (the composition of these solutions is given on p. 52). Oxygenation of the solution makes possible a modicum of oxidation, while an addition of glucose provides the cells with easily oxidated nutritive material. By perfusing the Ringer-Locke solution heated to 38° C through the vessels of an isolated heart of a homoiotherm it has been possible to retain its vital activity for 4 to 5 days.

The general laws governing the activity of excitable tissues are not infrequently studied on an isolated heart. It has been shown, for example, that the heart reacts to very slight variations in the composition of the fluid that bathes it. A slight change in the concentration of $K^{\cdot}$, $Ca^{\cdot\cdot}$, $H^{\cdot}$ and OH' sharply affects the activity of the heart. Because of this sensitivity of the heart to various agents the isolated heart is often used to characterize the effect of a number of drugs on living tissues. It should be remembered, however, that in the whole organism the relationships discovered in the isolated heart change and are disguised by new relations which are characteristic only of the whole organism.

Cardiac resuscitation. Professor A. Kulyabko performed a remarkable experiment (1902) which demonstrated that the human heart removed from the body several hours after death could begin to beat again if the Ringer-Locke solution heated to 40° C or defibrinated blood was perfused through its vessels.

It has been possible of late to restore in individual cases the function of the human heart which stopped because of a haemorrhage, electric shock, asphyxia and anaesthesia (V. Negovsky et al.). This has been accomplished by pumping oxygenated warm (37°C) blood at a pressure of 120 to 180 mm. Hg into the proximal end of some easily accessible artery (usually the femoral). This method brings the blood into the coronary vessels (vessels of the heart) and may lead to a restoration of the cardiac function (the injection of blood into the arteries simultaneously raises the tone of the vessels). Restoration of the heart function is possible only if the heart itself is not diseased.

Transplantation of the heart. Soviet investigators (N. Sinitsyn and V. Demikhov) recently succeeded in transplanting the heart of one animal into another animal of the same species. In his experiments on Amphibia Sinitsyn went so far as to have two hearts functioning in one frog—the frog's own and the transplanted heart. In mammals the transplanted heart "lived" only a few days.

Automatism and the Conducting System of the Heart

Automatism of the heart muscle. The excitability of tissues under the influence of their own impulses is called *automatism.*

We do not precisely know the nature or mechanism of the excitation originating in the heart itself. It is possible that an accumulation of carbon dioxide and carbonic acid and the resultant increase in the concentration of H-ions play a big part in the rhythmic excitation of the heart. A supposition was recently made that the rhythmic contractions of the heart were caused by production of acetylcholine in it.

The question has long been debated whether the automatism is to be ascribed to the muscular elements of the heart themselves (*myogenic theory*) or to the nervous elements (nerve cells and their processes) which are found in great numbers in the heart muscle and are particularly abundant among the elements of the conducting system described below (*neurogenic theory*). At the present time we must consider this controversy somewhat scholastic because in the heart, which is a single organ, all its structures are most closely coordinated. Under artificial conditions, greatly differing from the normal, the muscular elements of the heart may contract rhythmically without being influenced by impulses coming from the nervous structures. Thus, in the culture of muscle tissue grown outside the body it has been possible to observe rhythmic contractions of individual, isolated fibres of the heart muscle. During embryonic development the heart-beats of the foetus begin when histological examinations find no nerve cells or their fibres in the heart as yet. These experiments warrant the conclusion that automatism is in some measure inherent in the very muscular elements of the heart (especially the muscular elements of the conducting system).

The heart contains considerable accumulations of nerve cells known as the ganglia of Remak, Bidder, Ludwig and Dogiel. These ganglia receive nerve fibres from the brain. Thus, under normal conditions the nerve cells located in the thick of the heart muscle, chiefly in the region of the nodes of the conducting system, are under the influence of the central nervous system.

Since the nervous elements are more excitable than the muscle elements we may take it that under normal conditions excitation originates primarily in the nervous structures of the heart. At any rate, the nervous influences on the muscle tissue by affecting its metabolism and, consequently, its excitability may change the conditions for the origin of impulses which produce contractions of the heart. The slowing down of the heart rate under the influence of foxglove, widely used clinically, is probably due not only to the effect of this substance on the heart through the vagus (Chapter 13), but also to its effect on the nervous elements of the heart itself.

Conducting system of the heart. The heart is a complex organ whose musculature is represented by two different types of muscle elements: first, the elements of the muscular syncytium which make up almost the entire mass of the cardiac muscle; it is the muscle of the heart proper or the contracting myocardium; secondly, the heart has muscle fibres which are less striated and contain more sarcoplasm; these fibres belong to the so-called conducting system of the heart (sometimes designated as its specific musculature). The fibres of the conducting system have finer myofibrils and contain less glycogen than the fibres of the heart muscles proper.

The conducting system of the heart differs from the rest of the cardiac musculature by its greater excitability and higher conductivity. Certain features in the activity of this conducting system, built of muscle fibres among which there are numerous nerve cells, closely resemble the more general functions of the nervous system, i.e., especially high excitability with respect to some agents, and marked conductivity.

The accumulations of elements of the conducting system are encountered only at several points in the heart (Fig. 26). There is an accumulation of muscle fibres of the conducting system in the wall of the right atrium just under the epicardium between the point where the superior vena cava enters the atrium and the appendage of the right atrium (its fibres run in the direction of the inferior vena cava and the appendage of the left atrium). It is an accumulation of insufficiently differentiated muscle fibres abounding in sarcoplasm and is called the *sinu-atrial node*. The sinu-atrial node is homologous to the venous sinus of the lower vertebrates.

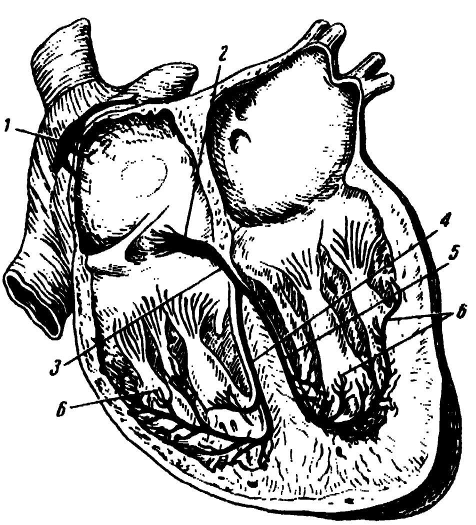

Fig. 26. Diagram of conducting system of the heart.

1 Sinu-atrial node; *2* Atrioventricular node; *3* Bundle of His; *4* and *5* Its right and left branches; *6* Terminal ramifications of branches of the bundle of His and Purkinje fibres.

The second accumulation of muscle fibres of the conducting system is located in the lower (i.e., closer to the ventricles) part of the atrial septum and partly passes through the ventricular septum into the ventricles. This accumulation is called the *atrioventricular node*. From this node a long and narrow muscular bundle, known as the *bundle of His*, runs down the ventricular septum. The bundle of His is a bridge between the atria and the ventricles. Everywhere else the atria are separated from the ventricles by a fibrous septum.

Penetrating into the ventricles in the septum which separates one ventricle from the other the bundle of His breaks up into two branches one of which runs along the internal surface of the left ventricle and the other—along the internal surface of the right ventricle. Breaking up into many ramifications the branches of the bundle of His make contact with the so-called Purkinje fibres which are located immediately under the endocardium of the ventricles and line nearly all of its internal surface. All these structures are also composed of muscle fibres belonging to the conducting system.

Both the atrioventricular and the sinu-atrial nodes contain a large number of nerve cells which give off axons that closely contact the muscles of the conducting system. These nerve cells receive fibres from the vagus. Thus, the sinu-atrial and the atrioventricular nodes* are not purely muscular, but neuromuscular structures. In certain pathological processes (for example, in a grave form of diphtheria) the morphological properties of the nerve cells of the sinu-atrial and the atrioventricular nodes undergo considerable changes (B. Lavrentyev).

Conduction of impulses in the heart. The process of excitation which spreads over the entire heart muscle during each normal cardiac systole normally begins in the structures of its conducting system. This excitation may also originate in the complex of the nervous and muscular structures of the conducting system automatically, i.e., in the absence of special external stimuli. The automatism does not manifest itself equally in the different elements of the conducting system. If we tie off the region of the venous sinus from the atria in the frog the atria and the ventricle cease to contract, while the venous sinus continues its contractions. Some time after application of the ligature below the venous sinus the atria and the ventricle resume their rhythmic contractions. However, the rhythm of contractions of the atria and the ventricle is now slower than that of the venous sinus. If we apply another ligature a little below the septum between the atria and the ventricle the latter stops while the atria continue contracting (experiments by Stannius). The first ligature made the propagation of the excitation from the venous sinus to the atria impossible and, therefore, the atria and ventricle stopped; it follows that the musculature of the atria with their atrioventricular node is less excitable and possesses lesser automatism than the sinu-atrial node (the venous sinus in frogs). The automatism of the atrioventricular node manifests itself some time after the separation of the venous sinus from the rest of the heart, but since this automatism is less pronounced than that of the sinu-atrial node the rhythm of the atrial and ventricular contractions turns out slower than normal. The second ligature separates the ventricle from the atrioventricular node and the ventricle stops. The automatism of the conducting system of the ventricle may manifest itself after a long pause and the ventricle will resume its contractions but at an even slower rate than those of the atria.

The result of the experiment could be explained by the fact that the ligature impairs the lower divisions of the heart and they temporarily lose all their excitability. This is disproved by the fact that electric or mechanical stimulation applied to the atria or the ventricle at the time of their stoppage after the Stannius ligature produces contractions; it follows that the tissues have retained their irritability and only the normal stimuli to rhythmic activity have dropped out.

A similar but chronical experiment was performed by Erlanger on homoiotherms. The bundle of His was crushed by a special clamp in dogs. In a number of cases the dogs survived the operation, but for the rest of their lives (up to one year) the rhythm of ventricular contractions constituted 25 to 40 per minute instead of the normal 90 to 100. This shows that when the bundle of His is destroyed the ventricles contract under the influence of impulses originating below the point where it was crushed.

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* In literature the sinu-atrial node is sometimes referred to as the Keith-Flack node and the atrioventricular as the node of Aschoff-Tawara.

The atrioventricular node or the bundle of His are sometimes affected in man as a result of pathological processes or injury. This is attended by phenomena of heart block (see below) which also testify to the fact that excitation normally begins in the sinu-atrial node.

The studies of the spread of electronegativity, which arises during excitation of the heart, also prove that the impulses of excitation take their origin in the sinu-atrial node. During each systole electronegativity originates primarily in the part of the right atrium which lies between the points of entrance of the superior and inferior venae cavae, i.e., where the sinu-atrial node is located.

Thus, excitation which is responsible for the contraction of the heart normally always begins in the sinu-atrial node; the latter is, as it were, the "pacemaker" of the heart. The rhythm of the contractions of the heart is subordinated to the rhythm at which impulses arise in the sinu-atrial node. Excitation is propagated from the sinu-atrial node to the atrial musculature and spreading over the latter at the rate of about one metre per second reaches the specific musculature of the atrioventricular node. In this node the spread of excitation is considerably slowed down and is transmitted to the bundle of His only 0.04 to 0.06 sec. after it has reached the atrioventricular node. Owing to this delay in the conduction of excitation through the atrioventricular node the systole of the ventricles normally always begins after the end of the atrial systole.

The delay in the propagation of excitation from the atria to the ventricles is hardly due to a slower spread of the impulses over the tissue of the atrioventricular node, because when a single electrical stimulus is applied directly to this node the response contraction of the ventricles occurs almost as fast as when the stimulus is applied to the ventricular myocardium. At the same time, when a stimulus is applied to the atria the response contraction of the ventricles occurs after an interval 4 to 5 times as long as when it is applied to the atrioventricular node. Udelnov believes that the atrioventricular delay is due to the same mechanism which explains the delay in the conduction of excitation through the synapses (p. 536). It is supposed that excitation in the atrioventricular node requires the development of a certain local negative potential in its atrial part. This negative potential in the atrioventricular node arises under the influence of the summation of the bio-current potentials reaching the atrial part of the node from the muscular bundles of the atrium which are not quite simultaneously excited. It takes time for the local negative potential to reach the degree at which the wave of excitation rises in the atrial portion of the node and spreads over the node (and is transmitted to the bundle of His and thence throughout the ventricular myocardium); this time constitutes a considerable part of the period of the atrioventricular delay.

From the atrioventricular node excitation spreads over the bundle of His and its branches with the velocity of approximately 0.75 (according to some data, even 3 to 4) metres per second rapidly reaching the Purkinje fibres which are, as it were, the terminal elements of the numerous ramifications of the bundle of His.

The Purkinje fibres not only form a network under the endocardium, but also pierce the ventricles and come in close contact with their musculature. This structure ensures a rapid spread of excitation over the muscular mass of the ventricle which possesses so little automatism that it, apparently, cannot be practically excited by itself. In A. Smirnov's laboratory it was observed under a microscope that contraction of the Purkinje fibres involves a contraction of the fibres of the ventricular musculature proper with which they come in contact. If the heart works under abnormal conditions the excitation does not pass from the Purkinje fibres to the fibres of the ventricular musculature proper; the former contract, while the latter remain immobile.

It takes excitation approximately 0.02 sec. to spread over the entire ventricular muscle. This time, apparently, corresponds to the interval between waves *Q* and *R* of the electrocardiogram. The interval between waves *P* and *Q* corresponds to the time it takes excitation to spread over the muscle of the atria and (mainly) to the time of the atrioventricular delay. This interval is normally 0.09 to 0.12 sec.

Heart block. Sharp changes in the conductivity and excitability of the elements of the conducting system impede the normal spread of excitation over the heart. The most essential changes in the relationship between the contractions of the atria and the ventricles occur in affections of the atrioventricular node or of the bundle of His. A prolongation of the atrioventricular delay is the first symptom of lowered conductivity of the atrioventricular node. In this case the electrocardiogram shows a lengthened interval between wave *P* and the ventricular complex *Q-T*. This interval may increase from 0.09 or 0.12 sec. to 0.3 or 0.4 sec. With such lowered conductivity of the atrioventricular node each of its excitations causes a still greater drop in conductivity which affects the speed at which the next wave of excitation spreads over the atrioventricular node.

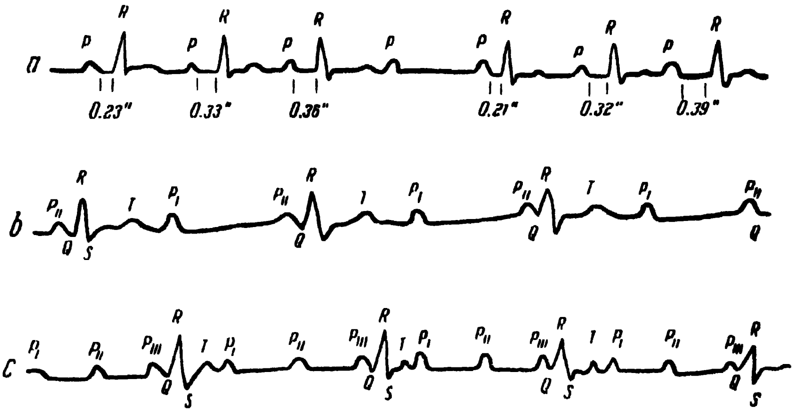

Fig. 27. Electrocardiogram of incomplete heart block.

Top (*a*)—ratio of number of atrial systoles to number of ventricular systoles is 4:3; middle (*b*)—2:1 and bottom (*c*)—3:1 (somewhat schematized).

Figure 30 shows that interval *P-Q* after the first (from the left) contraction of the atria equals 0.23 sec., after the second contraction—0.33 sec. and after the third contraction—0.36 sec. The fourth contraction of the atria fails to produce any contraction of the ventricles since the impulse from the atria reaches the atrioventricular node before the preceding impulse had passed through it. After such a "lapse" the conductivity of the atrioventricular node is restored since it has not been excited for a long time (about one second). In a new series of impulses passing through the atrioventricular node the time intervals between the beginning of the atrial and ventricular systoles are 0.21, 0.32 and 0.39 sec.; these are again followed by a "lapse." The ratio of the rhythm of the atrial contractions to that of the ventricles is 4 : 3 (sometimes 3 : 2).

If the conductivity of the atrioventricular node is more acutely impaired, the node, after letting the first impulse pass from the atria to the ventricles, is no longer capable of conducting the following impulse. In such cases every other excitation will fade in the atrioventricular node. Sometimes only every third impulse arising in the sinu-atrial node of the atria is conducted from the atria to the ventricles. The ratio of the atrial rhythm to that of the ventricles is then 2 : 1 or 3 : 1 (Fig. 27, *b* and *c*).

This lack of coincidence in the rhythm of the atrial and ventricular contractions which still retains a certain ratio in the rhythm of the atrial and ventricular activity is called a *partial (incomplete) heart block*. In the incomplete block the sinu-atrial node continues to be the pacemaker for the cardiac rhythm, but part of the impulses originating in this node cannot pass through the region of the atrioventricular block.

If some link in the conducting system is *totally* broken down the impulses originating in the atria fail to reach the ventricles and a *total heart block results*. This is observed when the bundle of His is injured or affected by a pathological process. In this case the automatism of the conducting system of the ventricles below the point of injury comes into play; this automatism is weaker than that of the sinu-atrial node. An *idioventricular* ("proper ventricular") rhythm of ventricular contractions, always slower than the rhythm of atrial contractions, which are subordinated to the sinu-atrial node, develops. The farther from the atrial portion of the atrioventricular node the bundle of His is affected the lower the rate of ventricular contractions.

If the impulses causing the contractions of the ventricles arise in the bundle of His, in the portions of the conducting system located lower, the rate of ventricular systoles may drop to 25 or 30 per minute. A complete lack of any correspondence between the rhythm of the ventricles and that of the atria is typical of a total heart block.

Phenomena of heart block (partial or total) are easy to discern in man by means of electrocardiographic studies which have become a clinical practice since the first decade of our century.

As early as the eighties of last century Pavlov described in detail the phenomena of heart block which he termed a "discord" in the activity of the atria and the ventricles. He observed this discord in experiments in which the heart was laid bare by opening the chest; in these cases the heart was in abnormal conditions which grew increasingly worse towards the end of the experiment. Having found phenomena of "discord" between the atria and the ventricles Pavlov simultaneously made an extraordinarily important discovery by establishing that stimulation of a certain nervous branch running to the heart, which he termed the intensifying nerve of the heart (p. 115), obviated this "discord."

Refractory Phase of the Heart, Extrasystole and Heart Block

In nervous and muscular tissue every stimulation is followed by a period of total nonirritability, called the *absolute refractory phase* or by a period of lowered excitability which only gradually returns to normal—the *relative refractory phase*.

The existence of the refractory phase is discovered when determining the minimal intensity of the stimulus capable of producing a second flash of excitation some time after the first. Even very strong stimulation (in the form of an induction discharge passed through the tissue) is incapable of producing a new impulse of excitation immediately after the first impulse; it follows that all this time the tissue is absolutely unexcitable (absolute refractory phase). Then excitability is gradually restored, though for some time it remains lower than normal; during this period of the relative refractory phase excitation may be produced only by applying a stronger stimulus than suffices to excite resting tissue. Following the relative refractory phase the tissue is for some time in a state of higher excitability.

The peculiarity of the refractory phase of the heart consists in the fact that here it lasts tenths of a second, whereas in skeletal muscles and in nerves its duration is measured by thousandths of a second (this is why the refractory phase was discovered in the heart first).

The refractory phase is easy to observe in the heart by stimulating the latter with induction current at different periods after the beginning of a systole. Fig. 28 shows a record of such an experiment performed by E. Marey (1863) who discovered the refractory phase of the heart. We see that no stimuli, however strong, produce any additional contraction of the heart (absolute refractory phase). At the end of the systolic period excitability is beginning to be restored. This is apparent from the fact that a strong stimulus applied at this time (relative refractory phase) produces an additional contraction or the so-called *extrasystole* (the stimulus must be strong because the excitability at this time is lowered). Moreover, the additional contraction begins at the time the heart has already partly relaxed.

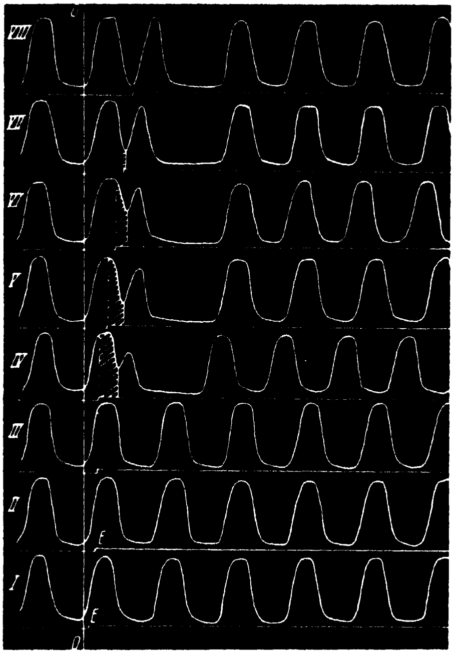

Fig. 28. Record of heart contractions in the frog showing refractory phase during each contraction (after Marey).

In each of above eight curves of heart contractions at moment marked by rise *(E)* of horizontal line (line of marker) surface of ventricle was stimulated by single shocks of induction current. In curves *I*, *II* and *III* this stimulation does not produce an additional, irregular contraction; from beginning of ventricular systole (vertical line *0-0*) to rise of line of marker in curves *I-III* the heart is inexcitable (refractory phase). In curves *IV*, *V*, *VI* and *VII* electric stimulation produces an additional contraction; latent period of this contraction, i.e., period between application of stimulus and additional contraction (see shaded areas) decreases as interval between additional stimulation and beginning of preceding systole grows longer. Curve *VII* shows considerable excitability of preparation, latent period is very short. "Compensatory phase" is also well seen in curves *IV-VIII*.

The refractory phase in each cardiac contraction is essential. The heart can perform its function of a pump, which drives the blood into the arterial system, only because its rhythmic contractions alternate with relaxations during which the heart is filled with blood. The refractory phase ensures the intermittence of excitation, while the duration of this refractory phase in the heart makes impossible the blending or fusing of its separate contractions into one continuous, tetanic contraction.

The duration of the cardiac refractory phase depends on the condition of the heart which is in large measure determined by the influences of the nervous system. All the phenomena connected with the duration of the refractory phase (for example, heart block [see above], fibrillation of the heart [see page 105]), therefore, largely depend on the influences of the nervous system on the heart.

Extrasystoles. Premature stimuli acting at the end of the refractory phase lead to premature systoles designated as extrasystoles. These stimuli may arise in the various portions of the conducting system of the heart. If a premature stimulus arises in the sinu-atrial node it leads to a premature cardiac cycle which occurs in the regular sequence of atrial and ventricular contractions. This sinu-atrial extrasystole is notable for the fact that the pause following this premature contraction of the heart is shorter than the pause between the usual contractions.

The extrasystole is frequently conditioned by an impulse originating in the atrioventricular rather than in the sinu-atrial node. From here the excitation may be propagated in both directions, producing a simultaneous contraction of the atria and the ventricles, or only through the bundle of His. In the latter case the extrasystole affects only the ventricles. If the regular systole of the atria coincides in time with the extrasystole of the ventricles the atrioventricular valves happen to be closed during the atrial systole. In this case the blood cannot flow from the atria into the ventricles and is forced into the veins as a result of which the venous flow to the heart temporarily ceases. If such occlusion of the atria repeats often circulation may be seriously impaired.

The ventricular extrasystole is followed by a prolonged pause before the next (regular) ventricular systole. This prolonged pause, called the *compensatory pause,* is due to the fact that the extrasystole, like the normal systole, leaves behind a refractory phase during which the impulse arising in the pacemaker at the regular flash of excitation cannot produce a ventricular systole. The ventricular systole which should occur because of the normal rhythm of the pacemaker, is extinguished by the refractory phase left by the extrasystole of the ventricles (see Fig. 28).

Cardiac Fibrillation and Flutter

Normally the entire musculature of the ventricles, like that of the atria, contracts simultaneously. Sometimes, however, in a pathologically changed heart the various muscle fibres of the atria or ventricles do not contract at the same time. Such individual contractions of the atrial or ventricular muscle fibres are called *fibrillation.*

If we produce ventricular fibrillation in an animal simply by subjecting it to intermittent electric current, the rhythmic heart-beats cease. The surface of the ventricles gives the impression of quivering and resembles ripples on the surface of water; the muscle fibres contract separately, individually. The fibrillar contractions cannot develop in the cavities of the section of the heart they affect (atria or ventricles) the pressure required to drive out the blood.

In fibrillations (and the more so in flutter) of the atria the electrocardiogram does not show the separate *P* waves, which precede the ventricular complex; it shows only incessant vibrations of the galvanometer string which testify to the chaotic and excessively frequent rise of excitation in different portions of the atrium.

The atrioventricular node and the bundle of His do not pass to the ventricles the large number of impulses that arise in the atria during their fibrillation. Under the influence of these frequent impulses the atrioventricular node is not excited rhythmically but at unequal intervals due, it must be assumed, to the varying durations of its refractory phase. A changeable rhythm of ventricular contractions is, therefore, observed in atrial fibrillation.

Atrial fibrillation and flutter not infrequently accompany a number of heart diseases and are not in themselves dangerous to life since the rhythmic contractions of the ventricles alone are enough to ensure circulation.

The mechanism of the origin of fibrillations and flutter of the atria and ventricles is not clear. A shortening of the refractory phase and the presence of some constant source of stimulation form the condition for the occurrence of fibrillations and flutter. The significance of the shortened refractory phase is confirmed by the possibility of eliminating the atrial flutter by pharmacological means which prolong the refractory phase of the heart. The role of "overstimulation" of the atrial muscle in flutter is testified to by the fact that the flutter is most frequently observed in mitral stenosis when the thin walls of the atria are distended by blood. A marked drop in body temperature (hypothermia) predisposes to cardiac fibrillations. Ventricular fibrillation is identical in its effect to a cardiac arrest and is always fatal if not discontinued by medical treatment. Cardiac fibrillation is responsible for a number of cases of so-called cardiac deaths and death resulting from myocardial infarction and electric shock. Fibrillation is also a dangerous complication in major operations, especially in cardiac operations. Fibrillation is sometimes stopped by direct massage of the heart, exposed during the operation, or by an injection of 2 to 5 ml. of a one per cent solution of potassium chloride or adrenalin. These measures may also aid in stopping fibrillation by other methods: passing through the heart (best through electrodes applied directly to the surface of the ventricles) one or several strong discharges of condensers (with a capacity of about 0.1 microfarads) charged with a current of several thousand volts (the force of the current passing through the heart must equal approximately 2 amperes). One or a few of these discharges (unlike alternating current which causes fibrillation) frequently (though regrettably not always) restores the normal rhythmic contractions of the heart. Though the mechanism of the action of the condenser discharge on fibrillation is not clear (inasmuch as the mechanism of their origin is not clear) this measure has made it possible to bring a number of people out of the state that threatened their life.

Correlation Between the Force of Stimulation and the Force of Contraction of the Heart

If we stimulate the frog's heart (stopped by means of Stannius' ligature) by induction shocks of different force we can see that the strength of contraction of the heart muscle is quite constant and does not depend on the force of the stimulation. We observe the same if we compare the height of the extrasystole produced by a single electric stimulation applied to the heart after the refractory phase (see Fig. 28). Subthreshold stimulation does not produce any contraction, but, after it has reached threshold intensity, no further increase in stimulation augments the force of the cardiac contraction. In other words, the force of the contractions of the heart does not depend in these experiments on the intensity of its artificial stimulation and cannot be increased by increasing the latter. This does not mean, however, that the force with which the heart contracts is always constant. We can only say that the force of cardiac contraction depends but little on the force of its stimulation and varies, as we shall see, with the condition of the heart muscle which constantly changes depending on all the conditions of cardiac activity.

Effect of the Initial Length of the Muscle Fibre on the Force of Its Contraction

The more the fibres of the heart are stretched before a contraction the greater, usually, the force of contraction of the heart muscle. This phenomenon is sometimes even referred to as the "law of the heart" (Starling), which is incorrect because it represents only a particular relationship and does not determine the entire activity of the heart; it holds true only under certain conditions (this relationship with similar limitations also holds true of the fibres of the smooth and the skeletal muscles).

*Muscle fibres are extensible and elastic.** *It is easy to see that the muscles (skeletal, smooth and cardiac) are extensible by measuring the length of a muscle supporting various loads.* The heavier the load supported by a muscle the more it stretches. The extensibility and elasticity of a muscle are variable values, however, depending on the condition of a muscle (for example, the extensibility of a muscle decreases during excitation).

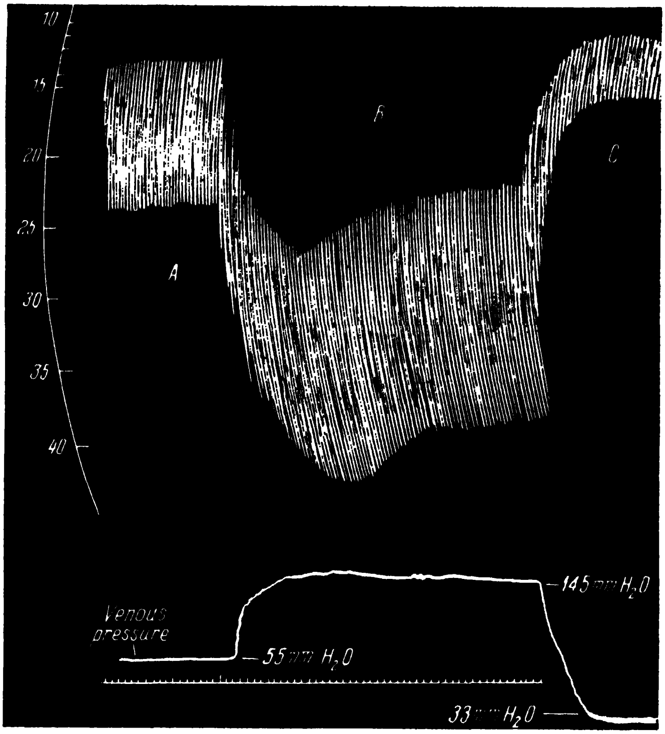

Fig. 29. Effect of heart distention on force of its contractions. cardiopulmonary preparation. Upper curve represent ontractions at different (*A*, *B*, *C*) pressures in ven its of curve correspond to volume of heart by end c oints by end of systole. Distance between upper an curve of heart contractions (range) corresponds to vo With higher pressure in vena cava (lower curve) vo ven into aorta increases and with fall in pressure in ven cava it decreases (after Starling).

The amount of blood filling the cavities of the heart is the physiological load which stretches the fibres of the heart muscle. The more blood accumulates in the heart during diastole, the more the cardiac muscle fibres stretch and the more vigorously they contract during the following systole. Figure 29 shows the result of an experiment in which the flow of blood to the heart was sharply increased by a small rise in venous pressure. We see that as soon as venous pressure rose the amount of blood forced out of the heart during systole increased. Owing to this a correspondence between the blood flow to and from the heart is quickly established.

It is impossible precisely to determine the extent of diastolic filling of the heart in man. A roentgenographic study of the diameter of the heart shows its distention. If the diameter has increased in a very short time it has, obviously, been caused by an increase in the diastolic filling of the heart. This does not make it possible, however, to obtain a quantitative characteristic of the distention of the heart. The relationship between the distention of the heart during diastole and the amount of blood forced out during the following systole has, therefore, been studied mainly on isolated hearts of homoiotherms by using the so-called cardiopulmonary preparation first proposed by I. Pavlov and N. Chistovich and later somewhat modified by Starling.

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* Extensibility implies the ability of a body to stretch, while elasticity means its ability to return to the initial length after the action of the stretching force is discontinued.

The heart in the cardiopulmonary preparation is usually not extracted from the thoracic cavity and is nourished by the blood which flows from a reservoir connected with the venae cavae by tubes. The contractions of the right heart drive the blood into the pulmonary artery (the pulmonary circuit is retained); in the lungs the blood is oxygenated and giving off its carbon dioxide flows into the heart as usual through the pulmonary veins. All the branches of the aorta, except the innominate artery, are tied off while from the innominate artery the blood flows through a system of tubes into the aforesaid artificial venous reservoir. Special contrivances make it possible to change: 1) the pressure in the venous reservoir which determines the amount of blood flowing to the heart and 2) the pressure in the aorta (or, to be exact, in the system of tubes connected with the innominate artery). By placing the heart in a closed capsule it is also possible to estimate its volume precisely. The amount of blood flowing to and from the heart is also taken into consideration.

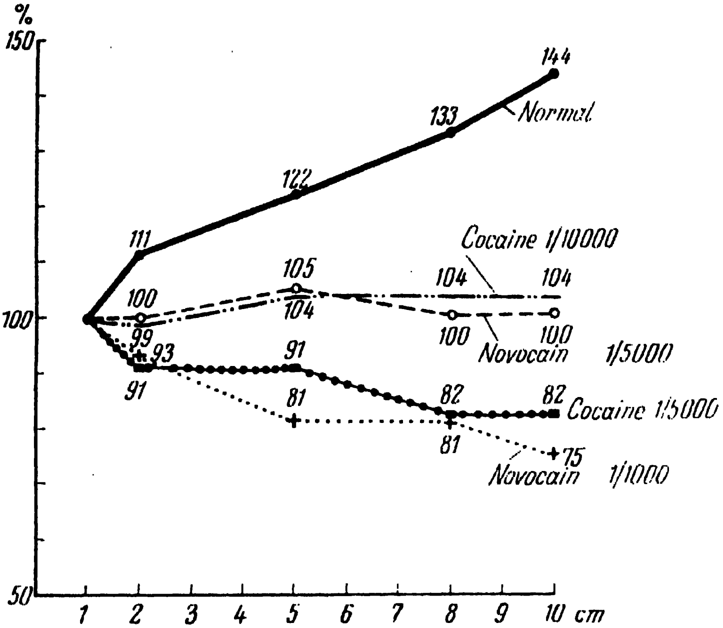

Fig. 30. Effect of rise in venous pressure (figures under abscissa) on normal systolic volume (continuous heavy line) and after addition of novocain or cocaine to Ringer's solution perfused through vessels of the frog's heart.

Figures under curves and on ordinate show systolic volume at high venous pressure of liquid in per cent to value of systolic volume taken at 100 during perfusion with Ringer's solution flowing into veins at pressure corresponding to 1 cm. H_2O.

The experiments with the cardiopulmonary preparation have shown that, for example, at a 2 mm. Hg pressure in the vena cava the heart of the dog weighing 56 gr. drove 4 ml. of blood into the aorta at each systole. But if the pressure in the vena cava rose to 9 mm. Hg, which sharply increased the flow of blood to the heart and, consequently, stretched its fibres accordingly, each systole drove 12 ml. of blood, instead of 4, into the aorta.

Work done under the supervision of the author has shown (see Fig. 30) that after perfusing Ringer's solution with an addition of novocain through the isolated frog's heart, no increase in the systolic emptying of the heart in response to a rise in the venous pressure is observed. At the same time novocain does not impede the increase in the contractions of the heart in response to an injection of adrenalin. The latter fact denotes that novocain does not paralyze the heart muscle itself. It is, therefore, natural to regard the reaction to stretching as a reaction involving the nervous structures of the heart.

With the same increase in the diastolic filling, i.e., the same distention, the increase in the contractions of the heart varies with its functional state which is determined by the sum total of reflex influences regulating cardiac function (see Chapter 13).

A strong heart can respond by a considerable increase in contraction even to a slight distention, whereas a weak heart can increase the force of its contraction but little even in response to considerable distention. From the point of view of Starling's thesis this in a certain measure explains why a trained athlete can do a good deal of physical work with a much lesser increase in the pulse rate than an untrained person. In a person with a weakened heart muscle the heart is distended even at rest because only in this state can it drive sufficient amounts of blood into the arteries. In muscular work the venous flow increases, the heart is distended even more but the force of its contractions increases only slightly. In this case the heart drives more blood into the arteries mainly by increasing the rate of its contractions.

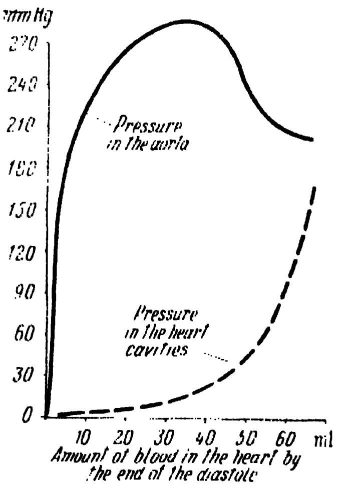

Fig. 31. Curve showing value of pressure in aorta by end of systole (solid line) compared with value of pressure in heart cavities by end of its diastole (dotted line). As heart distends pressure in aorta, developed during contraction of heart, rises and then begins to fall (after Best and Taylor).

Stretching of the heart fibres leads to an increase in their subsequent contraction only when they are stretched to a certain mean degree. If the fibres are stretched beyond a certain limit, which varies with the different functional states of the heart, the force of the subsequent contraction does not increase but, on the contrary, weakens (Fig. 31).

It should be emphasized that nervous influences (see below) determine the conditions for stretching the fibres of the heart muscle because they regulate the heart rate and thus condition the duration of the diastole and influence the distensibility of the heart. Furthermore, by changing all the properties of the heart the nervous influences also determine the nature of the reaction of the heart muscle to the stretching of its fibres (this has found full experimental confirmation in the recent investigations of L. Katz). Therefore, though the extent to which the heart fibres are stretched undoubtedly affects the force of their contraction, the intensity and nature of this influence depend on the functional state of the heart, which state is conditioned by the influences exerted on the heart by the whole body through and by the nervous system.

CHAPTER 13

REGULATION OF CARDIAC ACTIVITY

Its Significance and Mechanism

The circulation varies with every change in the body's environment and with the activity of its organs. The physiological processes determining these circulatory variations bear the common name of *circulatory regulation.*

Under normal conditions circulatory regulation is always a complex-reflex act in response to definite changes in the external environment and in the body itself, the activity of the heart usually altering simultaneously with the changes occurring in the state of the blood vessels.

Normally the regulation of cardiac activity ensures a correspondence between the amount of blood pumped into the vascular system per unit of time and the level of total metabolism which depends on the nature and intensity of the activity of the body's various organs and systems.

The enormous significance of the regulation of cardiac function is evident from the fact that, depending on the body's activity, the amount of blood pumped by the heart into the aorta per minute increases from 4 to 6 litres at complete rest to 20 to 35 litres during vigorous muscular work. This is caused by the increase in the volume of blood from 40 to 70 ml. to 100 to 180 ml. pumped into the aorta during each systole and to the change in the heart rate from 60 to 70 beats per minute to 180 to 240.

Regulation of cardiac activity is based on the reflex mechanism described on p. 41 and involves the efferent nerve fibres which innervate the heart and transmit to it the impulses reflexly arising in the nervous centres in response to stimulation of receptors. The study of the regulation of cardiac activity requires, first of all, knowledge of the nature of the influence exerted on the heart by the excitation of the different efferent nerve fibres which innervate it.

Morphology of the Efferent Cardiac Nerves

The heart receives endings of parasympathetic and sympathetic nerve fibres (Fig. 32). These nerve fibres belong to the vegetative nervous system which is characterized by the following morphological features: the axon of the nerve cell which is located in the central nervous system does not reach the cells of the innervated organs, but ends near the nerve cells of some particular ganglion of the vegetative system; this is why it is called a *preganglionic fibre.* The axons of the nerve cells of the ganglion which directly contact the cells of the innervated organ are called *postganglionic fibres.*

After leaving the medulla oblongata the parasympathetic fibres of the vagus, which innervate the heart, travel in the common trunk of this nerve running alongside the trachea in the neck. Sympathetic nerve fibres also enter this nerve on various levels. As the vagus enters the thoracic cavity it branches off into (see Fig. 35) the superior, middle and inferior cardiac nerves in which the preganglionic fibres of the vagus are often mixed with the postganglionic sympathetic fibres. Upon entering the heart the parasympathetic fibres terminate near nerve cells which form a number of clusters (nervous nuclei of Dogiel, Remak, Bidder and Ludwig). The main mass of these cells is located in the sinu-atrial and the atrioventricular nodes of the conducting system of the heart (p. 99) while the relatively short axons of these nerve cells of the heart directly contact its musculature—the fibres of the specific musculature of the conducting system and probably the fibres of the cardiac muscle proper. The nerve fibres entering the heart run mainly along the atrial septum and form the intracardiac plexus.

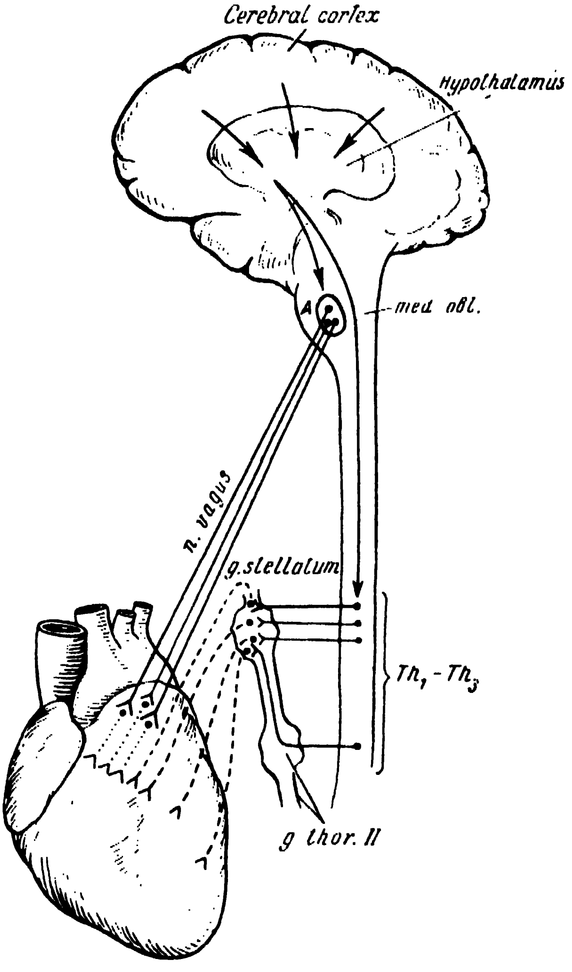

Fig. 32. Diagram of cardiac innervation.

A nucleus of cardiac fibres of vagus in medulla oblongata; Th_1-Th_3 – segments of spinal cord containing cells which give off sympathetic nerve fibres to heart; *g.thor. II* second thoracic sympathetic ganglion. Solid lines indicate preganglionic fibres of vagus and sympathetic nerves; dotted line – postganglionic fibres of vagus in heart; broken lines postganglionic sympathetic fibres running to heart. Arrows show influence of cerebral cortex relayed through hypothalamus to nuclei of vagus and of sympathetic cardiac nerve fibres.

The preganglionic sympathetic nerve fibres of the heart (see Fig. 32) are axons of nerve cells located in the grey matter of the lateral horns of three thoracic segments of the spinal cord. Upon leaving the spinal cord with the three upper thoracic ventral roots they enter the sympathetic chain and terminate mostly near the cells of the upper thoracic sympathetic ganglion called the stellate ganglion (*gangl. stellatum*). The axons of the cells of the ganglion, i.e., the postganglionic sympathetic fibres (as well as some preganglionic fibres which run uninterrupted through the stellate ganglion and terminate near the cells of the cervical node) travel with the two neural branches which surround the subclavian artery and form the so-called *loop of Vieussens* (*ansa Vieussenii*). After passing through this loop the postganglionic sympathetic fibres enter the rami of the cardiac nerves frequently mixing with the fibres of the vagus. Upon entering the heart the postganglionic sympathetic fibres terminate near the fibres of the muscular syncytium of the heart with the sympathetic fibres also terminating in the ventricular muscle.

The aggregate of nerve cells in the medulla oblongata, whose axons form the fibres of the vagus which innervate the heart, are often referred to as the *centre* or the *nucleus of the cardiac fibres of the vagus*; the nerve cells forming the preganglionic sympathetic fibres which innervate the heart are called the *centres* or *nuclei of the cardiac sympathetic fibres.*

Effect of Vagal Stimulation on the Heart

Inhibiting influence of the vagus on the heart. In 1845, the Weber Brothers found that a sufficiently strong stimulation of the vagus stopped the heart, while a weaker stimulation of the same nerve reduced the heart rate. This was the first case of inhibition discovered in physiology.

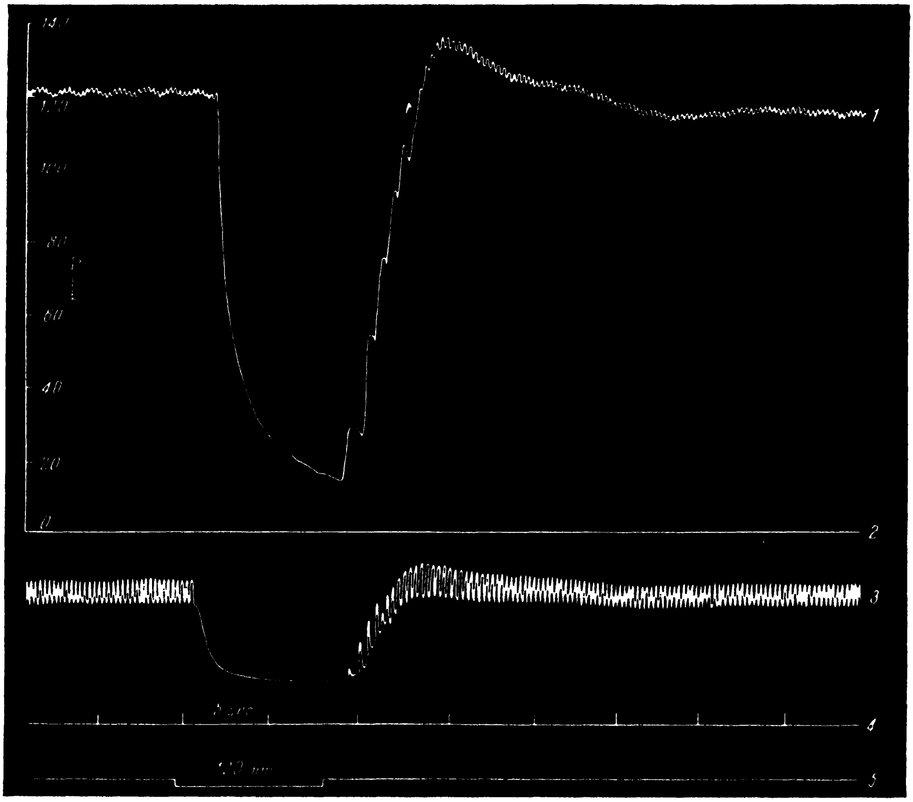

Fig. 33. Effect of stimulation of distal portion of vagus on cardiac activity in the dog. Cardiac activity is measured by changes in blood pressure recorded by mercury manometer (curve *1*) and by readings of spring manometer (curve *3*). Stimulation of vagus with coils 120 mm. apart is registered on line *5*.

Fig. 33 shows the effect of vagal stimulation on the dog's heart. To avoid opening the chest the heart-beats in this experiment were recorded by recording the blood pressure which reflects the changes in the work of the heart since a stoppage of the heart or a decrease in the heart rate infallibly produce a drop in blood pressure. In Fig. 33 we see that the curve of the record of blood pressure sharply drops as soon as the vagus is stimulated, *while* the pulse waves corresponding to each contraction of the heart become very rare. Fig. 34 shows the same effect of vagal stimulation on the frog's heart.

Outwardly the inhibition appears to be a return to rest since at this time the function of an organ either weakens or ceases. But while an organ is at rest because it is not stimulated (since nothing conditions its excitation) a state of inhibition, on the contrary, results only from stimulation which suppresses the effect of excitation. To bring an organ out of its state of rest requires some sort of a stimulus; to bring an organ out of its state of inhibition requires, on the contrary, a cessation of the action of the stimulus which produced the inhibition. Consequently, the process of inhibition cannot be regarded as a return of the organ to a state of rest. Inhibition is an active process which suppresses the organ's functions.

The heart is inhibited through excitation of the vagus. When we artificially stimulate the vagus we produce in its fibres, especially in the fibres running to the heart, a process (impulses) of excitation. This excitation of the cardiac fibres of the vagus does not differ from the excitation of any other nerve fibres, for example, the motor fibres which transmit the excitation to a skeletal muscle. However, excitation of the vagus inhibits the activity of the heart.

The vagal fibres running to the heart are preganglionic fibres. The impulses propagated along the fibres of the vagus are transmitted to the heart muscle through the cells of the nervous ganglia located in the heart. We can easily demonstrate this by using nicotine which paralyzes the transmission of excitation from the preganglionic fibres of the vegetative nervous system to its postganglionic fibres. If we paint the heart with a solution of nicotine, after a short phase of slower heart rate (due to the initial exciting effect of this poison on the ganglionic cells) stimulation of the vagus will not inhibit the heart. But if we follow this by stimulating the heart with a weak electric current we shall produce a typical vagal effect—the heart will stop because the electric current will now act directly on the postganglionic fibres running in the cardiac muscle. It may be assumed, however, that the electric stimulation inhibits the heart by acting directly on its muscle. To verify this the heart is painted with a solution of atropine, a poison which paralyzes the transmission of excitation from the endings of the postganglionic fibres to the organ. If we stimulate the heart with electric current after this there is no inhibition. It follows that nicotine made the transmission of excitation from the preganglionic fibres to the postganglionic impossible, whereas atropine was responsible for the impossibility of transmitting the excitation from the endings of the postganglionic fibres to the effector.

Chronotropic and inotropic action of the vagus on the heart. The inhibiting action of the fibres of the vagus on the heart is characterized by a reduced heart rate and a reduction in its contractile force. The influences on the rhythm of cardiac contractions are called *chronotropic influences* (from the Greek word "chronos"—time), with the influences slowing down the heart rate designated as *negatively chronotropic,* while the influences accelerating the heart are referred to as *positively chronotropic.* The influences on the force of the contractions are termed *inotropic influences* (from the Greek word "inos"—force); the *positively inotropic* influences increase the force of contractions and those that weaken it are *negatively inotropic.* The effect of the excitation of the vagus—the change in the heart rate and in the force of the heart-beats—can be in a certain measure divided, as it was for the first time demonstrated by I. Pavlov in 1882.

Only the summary result of the action of the vagi on the heart was known before Pavlov, and the attention was mainly focussed on the cardiac arrest and the slowing down of the heart rate when these nerves were stimulated. By stimulating various fine nervous branches separated in the cardiac plexus Pavlov found branches of the vagus whose stimulation produced only a weakening of the heart-beats without reducing the heart rate.*

The postganglionic fibres of the vagus terminate in the sinu-atrial and the atrioventricular nodes and in the atrial muscle. According to a number of morphologists the ventricular muscle has no parasympathetic nerve fibres and the weakening or cessation of the ventricular systoles during stimulation of the cardiac fibres of the vagus are, therefore, due either to a suppression of the impulses arising in the sinu-atrial node, the normal "pacemaker" of the cardiac rhythm, or to the suppression of the conduction of the impulses through the atrioventricular node. After cutting the bundle of His stimulation of the vagi usually no longer stops or slows down the ventricular contractions.

The right vagus is connected chiefly (through the nerve cells of Remak's ganglion) with the sinu-atrial node and the atrial muscle. Its stimulation, therefore, leads mainly to a slowing down of the heart rate. The left vagus gives off more branches to the atrioventricular node; its excitation depresses the conductivity of this node, stopping the heart or decreasing the force of the heart-beats. D. Polumordvinov demonstrated (1909) that stimulation of the trunk of the vagus in the frog resulted in a pure negative chronotropic effect, while stimulation of the branches of the intracardiac plexus led to a weakening of the cardiac contractions (Fig. 34).

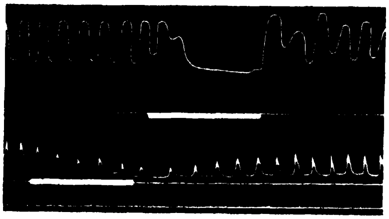

Fig. 34. Effect of stimulation of vagus (upper record) and of nerves of deep internal nervous plexus of heart (lower record) on contraction of the frog's heart.

Period of stimulation is marked by heavy line. Time intervals — 1 second (after D. Polumordvinov).

It was recently discovered (T. Turpayev) that the poisons which blocked the sulfhydryl groups (for example, sublimate) removed the negative inotropic effect of the stimulation of the vagus on the frog's heart without eliminating the influence of this stimulation on the heart rate. This indicates that there are differences in the chemical dynamics of the processes involved in exerting the influences of the vagus on the various aspects of cardiac activity.

Dromotropic and bathmotropic influences of the vagus. The vagus also affects the excitability of the heart by exerting a *bathmotropic influence*, and the velocity of the spread of excitation over the heart, i.e., conduction, by *dromotropic influences*.

To produce by means of electric current a contraction of the heart inhibited by excitation of the vagus requires a higher current tension than is needed to produce an extrasystole of a normally contracting heart; in this case excitation is provoked by the action of a strong current on the heart muscle over a shorter period of time. The *chronaxia* of the heart (Chapter 49) inhibited by excitation of the vagus is, thus, *shortened*. During excitation of the vagus the refractory phase of the heart also shortens, while the speed at which excitation spreads over the heart increases revealing a positive dromotropic effect of the vagus which, incidentally, is not acknowledged by all investigators. However, the question of bathmotropic and dromotropic influences of the vagi on the heart has been studied less than that of the chronotropic and inotropic influences.

Ventricular escape. If the vagus is strongly stimulated for a relatively long time the ventricles of the heart which stopped in the beginning start contracting again, though at a slower rate. It follows that despite the continuing stimulation of the vagus the ventricles partly free themselves from its inhibiting influence. This weakening of the inhibiting vagal influence on the heart during the invariable stimulation of the latter is designated as *escape* of the heart from the influence of the vagal impulses.

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* The work of I. Pavlov in ascertaining the effect produced on the heart by the stimulation of various nervous branches of the cardiac plexus is in itself a model of very fine analytical investigation; however, Pavlov undertook this work in order to study so integral a process as the maintenance of a constant value of arterial blood pressure. Pavlov observed that "...frequently a very substantial slowing down (of the heart rate) is not accompanied by any drop (in blood pressure) and vice versa." (I. Pavlov, *Complete Works*, Vol. I, p. 364; the words in parentheses are ours.) The analysis of these facts led to the discovery of new efferent nerves of the heart which control the force of its contractions and, thus, sharply affect the blood pressure.

The weakening of the inhibiting effect produced on the heart by excitation of the vagus during its prolonged stimulation considerably reduces, and perhaps excludes, the possibility of an irreversible arrest of the heart during reflex excitation of the vagus. The mechanism of the phenomena of escape is not clear as yet. An essential part is, apparently, played by the fact that excitation of the vagus often renders the heart more sensitive to the influences (see below) transmitted to it along the sympathetic nerve fibres which intensify the activity of the ventricles. No escape phenomena have been discovered in the atria.

Influence Exerted on the Heart by Stimulation of Its Sympathetic Nerve Fibres

The sympathetic nerve cells exert an influence on the heart outwardly antagonistic to that of the vagus; stimulation of the sympathetic fibres accelerates the heart and makes it beat more forcefully. It follows that the impulses running to the heart along the sympathetic fibres usually act on the heart positively chronotropically and positively inotropically.

Pavlov's investigations (1882-87) analysing the influences of the different nervous branches of the cardiac plexus (Fig. 35) revealed two types of fibres exerting positive influences on the heart; stimulation of some leads only to an acceleration of the heart and a shortening of the cardiac pause without affecting the force of the ventricular contractions; stimulation of others does not alter the heart rate but makes the heart beat much more forcefully and shortens each systole; stimulation of these accelerator fibres prolongs the cardiac pause by shortening the systole. Pavlov, thus, established the "... existence of special efferent nerves which increase the work of the heart and which, therefore, quite deserve the name of intensifying nerves." *

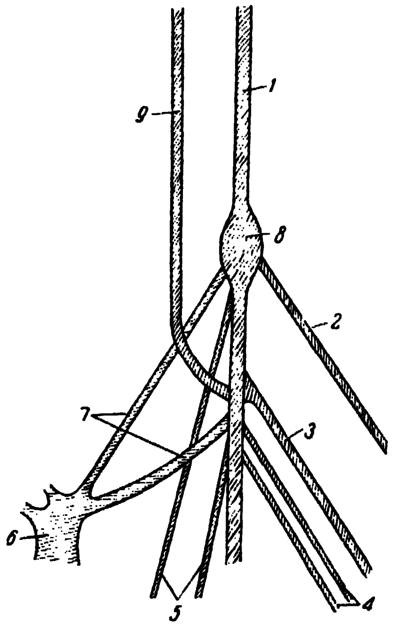

Fig. 35. Diagram of cardiac nerves (after I. Pavlov).

1— trunk of vagus (it also contains sympathetic fibres); *2-5* branches of cardiac nerves; *6*— stellate ganglion and *8*— inferior cervical sympathetic ganglion; *7*— branches of loop of Vieussens (Vieussens' ansa); *9*— recurrent branch of laryngeal nerve.

Stimulation of the accelerator branches does not increase the pressure under which the blood is driven into the arteries (blood pressure). Stimulation of the reinforcing nerve sharply increases the force of ventricular contractions and, as a rule, leads to a rise in blood pressure (Fig. 36). If the accelerator nerve fibres alone are stimulated the heart cannot long contract in the rhythm forced on it by the stimulation of the accelerator fibres. A lack of harmony in the function of the atria and the ventricles soon manifests *itself—the former maintain a rapid rhythm, while the ventricles contract once for every two (or three) contractions of the atria (partial heart block). If the intensifying* branch is now stimulated in addition to the accelerator fibres the rhythm of the ventricles adapts itself to the accelerated rhythm of the atria and the phenomena of disharmony (block) are eliminated. A similar elimination of the block by stimulation of the intensifying nerve is observed if the heart block results from keeping the heart for a long time under abnormal conditions created, for example, by opening an animal's thorax in an acute experiment; in Pavlov's experiments the heart worked under these conditions without stimulation of the intensifying nerves for no more than 30 to 45 minutes; with the stimulation of the intensifying nerve repeated periodically the heart retained its efficiency for hours under the same conditions. In addition, stimulation of the intensifying nerve augmented the force of the ventricular systoles to such an extent that the volume of blood driven into the aorta during each systole increased four- to sixfold compared with the volume of the blood pumped by the tired heart before the stimulation of the intensifying nerve (according to Pavlov the intensifying nerve produces a weaker effect on the "fresh" heart).

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* I. Pavlov, *Complete Works*, Vol. I, p. 416.

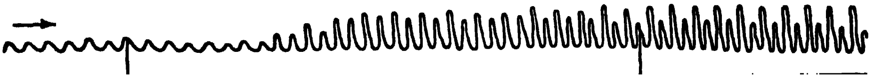

Fig. 36. Effect of stimulation of accelerator nerve on contractions of the dog's heart. Vertical lines mark stimulation of branch of cardiac plexus containing fibres of accelerator nerve (after I. Pavlov).

According to Pavlov the nerve fibres which accelerate and intensify the heartbeats must be referred to the sympathetic nerves (stimulation of the vagal trunk in the neck produced the effect of stimulation of the intensifying nerve only once or twice in hundreds of his experiments). Pavlov emphasized that the intensifying fibres run along the loop of Vieussens. The close relation of the intensifying nerve fibres to the sympathetic system is also attested by the fact that the effect of their stimulation is fully retained after the animal is injected atropine. Finally, their relation to the sympathetic system is confirmed by a long latent period and a protracted aftereffect which are observed when the intensifying nerve is stimulated.

In discussing the mechanism of the action of the intensifying nerve Pavlov wrote (1888): "We must actually characterize our intensifying nerve as the one that generally enhances all the vital properties of the ventricular muscle"* (its excitability, conductivity and contractility). Pavlov believed that the intensifying nerve affected the heart *trophically,* i.e., primarily influenced the metabolism, the nourishment of the heart. He supposed that excitation of the intensifying nerve brought more nutritive material to the tissues and created conditions for better utilization by the heart of the substances it assimilated. We may assume that in this case different conditions are set up in the very tissue of the heart for the action of enzymes, these conditions ensuring an increased liberation of energy at a higher efficiency, i.e., with the transformation of a greater part of the liberated energy into mechanical work; the replenishment of the substances utilized during contractions is increased at the same time.

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* I. Pavlov, *Complete Works,* Vol. I, p. 454.

Pavlov's idea of the trophic effect of the intensifying nerve on the heart was confirmed by the study of N. Podkopayev who established that the dog's heart deprived of its sympathetic innervation could not, like the normal heart, retain its constant weight for a long time during total starvation of the animal. Under these conditions the normal heart uses the proteins, fats and carbohydrates brought by the blood from the skeletal muscles and the connective tissue and seems to nourish itself at the expense of the organs less essential to life. After removal of the stellate ganglia, i.e., disconnecting the sympathetic innervation of the heart, this regulation of metabolism and nourishment is deranged and the heart in large measure loses its ability to retain and replenish its reserves of nutritive material during total starvation of the organism.

Humoral Mechanism of Nervous Influences on the Heart

Studies of the action of the postganglionic parasympathetic and sympathetic fibres on the heart led to a very important discovery which revealed the mechanism of the nervous influences on the effectors. In 1922 O. Loewi demonstrated that when the postganglionic fibres of the vagus were stimulated a chemical substance was liberated in their endings and this substance acted on the heart just like excitation of the vagus. During excitation of the sympathetic nerve a substance is liberated in the postganglionic sympathetic endings and this substance affects the heart the same as does excitation of the sympathetic fibres. If Ringer's solution which bathed the frog's heart during its arrest produced by vagal stimulation is collected and added to the fluid flowing through the isolated heart of another frog the contractions of this heart slow down and weaken as they do after stimulation of the vagus (Fig. 37). Consequently, the effect of vagal excitation can be produced humorally by the action of the chemical agents contained in the fluid which bathed the heart inhibited by the excitation of the vagus.

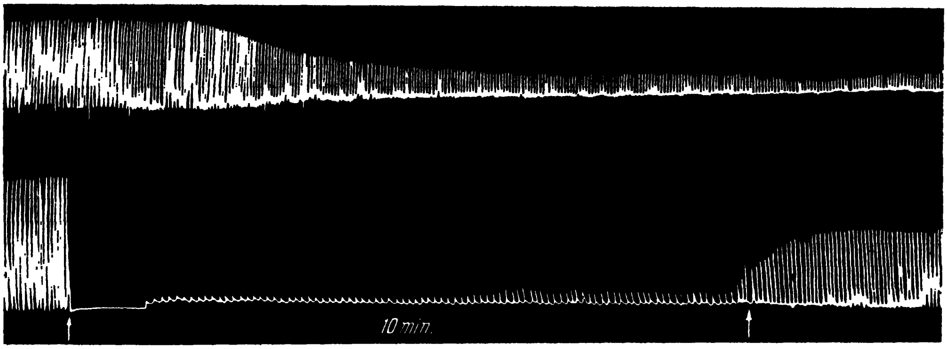

Fig. 37. Humoral transmission of inhibiting effect of vagus on the heart.

Bottom record of contractions of the frog's heart during (see arrows) stimulation of its vagus. Top—simultaneous record of contractions of another heart through which physiological solution flowing out of first heart is perfused (after K. Koshtoyants).

We can observe an acceleration and intensification of the work of the heart under similar experimental conditions by perfusing it with Ringer's solution which bathed the heart whose contractions were accelerated and intensified by stimulation of its sympathetic nerve fibres (Fig. 38).

It follows that during stimulation of the nerves, which innervate the heart, certain substances are produced in their postganglionic endings and these substances influence the heart in the same way as does excitation of the corresponding nerves. During excitation of the postganglionic parasympathetic fibres of the vagus acetylcholine is liberated at their endings. The compound produced at the endings of the postganglionic sympathetic fibres during their excitation is extraordinarily close to adrenalin (it is sometimes called *sympathin*). Neither of these compounds, especially acetylcholine, is stable. Acetylcholine is very easily destroyed by a special enzyme called cholinesterase. This is precisely why the effect of vagal excitation wears off very soon after stimulation of the latter is stopped.

Acetylcholine and adrenalin are often called humoral *mediators* of nervous excitation. They are formed at the parasympathetic and sympathetic endings in negligible quantities (thousand-millionth fraction of a gram).

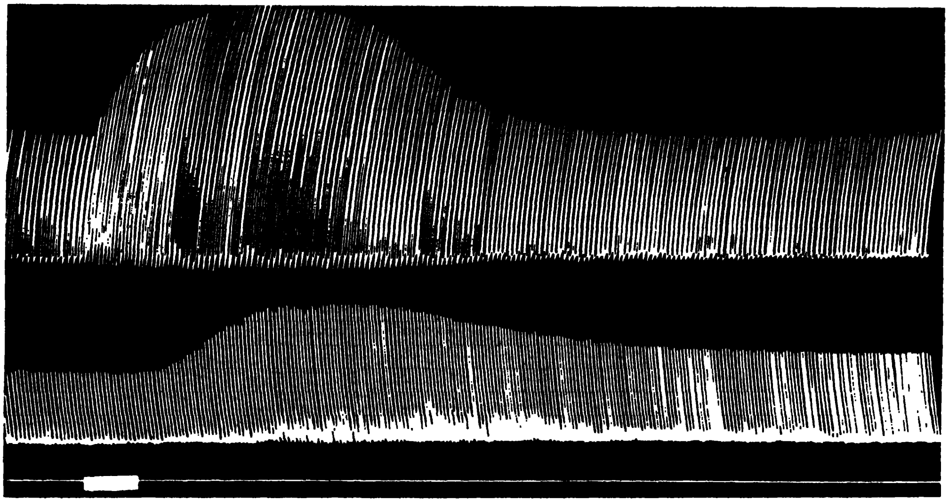

Fig. 38. Humoral transmission of effect of stimulating sympathetic nerve fibres of the heart.

Upper record shows acceleration of contractions of the frog's heart in response to stimulation of its sympathetic fibres by induction current (period of stimulation is shown by white band on lower line). Lower record shows simultaneous contractions of second heart through which Ringer's solution flowing from the first heart is perfused (after V. Boldyrev).

But these substances are extraordinarily active; for example, about 1:10,000,000 concentration of acetylcholine is enough to stop the heart. It is very probable that the action of the nerve impulses on the working organs innervated by the vegetative nervous system always involves acetylcholine liberated at the endings of the fibres of the parasympathetic system and adrenalin formed at the terminal apparatus of the postganglionic fibres of the sympathetic system. Nervous excitation leads to the liberation of these compounds at the nerve endings and these compounds, influencing the effector, condition the changes in its activity. Such is the chemical theory of transmission of nervous influences.

K. Koshtoyants and his associates recently demonstrated the connection between the action of the chemical factors of nervous stimulation and the metabolism of the innervated organ. Thus, for example, in the frog when the metabolism of the heart is affected by poisons (sublimate and some organic compounds of trivalent arsenic) which block the sulfhydryl groups (—*SH*) the myocardium loses its sensitivity to acetylcholine and to impulses from the vagus but retains the contractile properties of its muscle fibres. If normal metabolism of the heart is restored by adding compounds containing free *—SH* groups (for example cysteine) to the fluid passed through the heart the depressing effect of acetylcholine on the heart is again restored and stimulation of the vagus again produces the negative inotropic effect.

Tone of the Cardiac Nerves

The fact that the vagus contains fibres whose stimulation weakens and slows down the contractions of the heart (the weakening and decelerating fibres) does not of itself show how and when the vagus affects the heart under normal conditions. It is important to know not only that this nerve *can* inhibit the heart; it is even more important to know when and to what extent this inhibition of the heart occurs. The experiments described below help essentially in answering these questions.

Effect of suppressing vagal influence on the heart. If we cut both vagi in the dog the heart rate will immediately increase 1 1/2 to 2 1/2-fold (Fig. 39). The same thing is observed in man when the action of the parasympathetic nervous system on the heart is temporarily discontinued by atropine, a pharmacological agent, which makes the transmission of excitation from the postganglionic fibres of the parasympathetic system to the effectors they innervate impossible (atropine stops the action of acetylcholine, the vagus mediator, on the heart). A strong acceleration of the heart rate is observed after a subcutaneous injection of 2 to 3 mg. of atropine; the heart rate usually reaches 140 to 180 beats per minute.

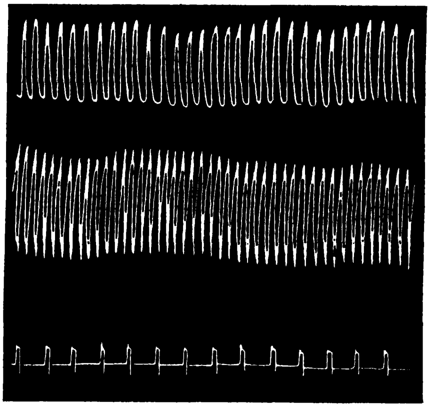
Fig. 39. Record of the dog's heart rate: top—before cutting, centre—after cutting both vagi. Bottom—time intervals (2 seconds).

Since suppression of vagal influence accelerates the heart rate we must take it that the fibres of the vagus running to the heart propagate nerve impulses continuously. It follows that the fibres of the vagus, which inhibit the heart are constantly in a state of certain excitation which is not strong enough to stop the heart but which suffices in some measure continuously to decelerate the cardiac rhythm.

Tone of the vagal centre. A prolonged excitation which is not attended by fatigue is called *tonic*. The state of incessant, now increasing and now decreasing, excitation of the neurons of the vagus which innervate the heart is referred to as *vagal tone*. This excitation of the vagi uninterrupted, but varying in force, inhibits the work of the heart in the same measure.

Thus far we have only elaborated the problem pertaining to the tone of the vagal neurons whose fibres conduct the impulses which decelerate the heart rate. We do not know whether the neurons, whose axons transmit to the heart the impulses which weaken cardiac contractions, have any tone; the solution of this problem presents difficulties.

There are cases in which for as yet unknown reasons the tone of the vagal neurons, which inhibit the heart, in man suddenly weakens. This results in an uncommonly strong acceleration of the heart (up to 160 to 180 and more contractions per minute at rest) which is called *paroxysmal tachycardia.* This paroxysm is sometimes stopped by measures which increase the vagal tone.

The tone of the vagal neurons which innervate the heart is, undoubtedly, due to the constant impulses of excitation in the nerve cells of the nucleus of the vagus whose axons run to the heart. These impulses of excitation which condition the tone of the neurons of the vagi innervating the heart arise reflexly, mainly under the influence of impulses from the vascular interoceptors (Chapter 17). Acceleration of the heart, which occurs in muscular work and in emotional states, is always connected with a decrease in the tone of the vagal neurons which inhibit the heart (the tone of the sympathetic neurons innervating the heart is usually increased at the same time; see below).

In newborn children the vagal tone is weak or absent which explains why they have a quick pulse (130 to 140 beats per minute). The cardiac fibres of the vagus acquire tone during the first weeks of life.

Certain pathological processes are accompanied by a considerable rise in the tone of the vagal neurons which innervate the heart and are, therefore, characterized by a slower heart rate. The increase in the tone of the vagi is especially characteristic in hypertension of the cerebrospinal fluid and in cerebral tumours. Certain chemical agents injected into the blood also raise vagal tone (for example, the active principles of foxglove). It is possible that in these cases the increased vagal tone is due to a direct effect of the mechanical stimulation (pressure) and the chemical agents on its nerve cells. Normally it is the reflex influences that play the decisive part in regulating the tone of the vagus.

Tone of the sympathetic cardiac fibres. The cells from which sympathetic fibres run to the heart also have a certain tone. This problem has been studied less than the problem of vagal tone, but it has been found that after extirpation of the stellate ganglia, i.e., after almost completely depriving the heart of its sympathetic innervation, the heart rate slows down. After depriving the heart of its sympathetic innervation the rhythm of the heart-beats (in dogs) is 15 to 25 per cent lower than normal.

The tone of the intensifying nerve has not been sufficiently studied.

Interrelation of the Vagal and Sympathetic Influence on the Heart

The centres of the cardiac fibres of the vagus and the sympathetic nerves are so interrelated that a considerable increase in excitation of one of them usually occurs simultaneously with a decrease in excitation of the other. If, for example, the tone of the vagal centre decreases in muscular work the tone of the cardio-accelerator centre and of the intensifying nerve increases. In these cases the acceleration and intensification of the heart-beats are achieved because of the simultaneous decrease in the inhibitory influences of the vagus and increase in the stimulatory influence of the sympathetic innervation.

If the inhibitory influences transmitted to the heart along the fibres of the vagus are stopped and the accelerating effects of the sympathetic system are retained, the heart rate increases much more than when both the sympathetic and vagus innervations of the heart are suppressed. This corresponds to clinical observations which have shown that after the vagal influence of the heart is suppressed in people by atropine the emotional excitement, which stimulates the sympathetic innervation of the heart, accelerates the cardiac rhythm still more. However, during muscular and mental rest the influence of the tonic excitation of the vagal neurons, which innervate the heart, prevails over the tonic excitation of the sympathetic system; a completely denervated heart beats much faster than normal.

Normal work of the heart is determined by the interaction of the nervous influences exerted on it. Moreover, it should be remembered that different nerve fibres influence various aspects of the work of the heart ensuring precisely by their joint action the most complete adjustment of the heart to the different conditions of bodily activity. The fibres of the vagus, which inhibit the activity of the heart, are not antagonists of the intensifying fibres of the sympathetic nerve by the final effect they produce on the whole body. Pavlov found that retardation of the systoles produced by stimulation of the vagus may lead to a rise in blood pressure when the latter is for some reason dropping. This is explained by the fact that during excitation of the vagus the pause between the systoles is prolonged which aids in neutralizing the biochemical changes produced by each contraction of the heart; the contractions become stronger. This is why Pavlov said that the inhibitor fibres of the vagus "were the regulators of the heart's rest." Consequently, according to its final effect, the action of the sympathetic and the parasympathetic fibres of the heart is in this case not antagonistic but synergic: by slowing down the heart a certain degree of excitation of the vagal neurons leads to an increase in the filling of the heart with blood during diastole and to an intensification of the following systole.

The relation between the influences of the fibres of the vagus and the sympathetic nerves on the heart is regrettably still investigated only through studies of the heart rate. The force of the cardiac contractions, a no less important factor than their rhythm, has largely been neglected by the investigators of cardiac innervation partly, possibly, because it is technically much more difficult to estimate the force of the heart-beats (especially in a chronic experiment) than of the heart rate.

Inhibition of the rhythm of heart-beats, when certain fibres of the vagus are stimulated, and acceleration of the heart rate during stimulation of certain fibres of the sympathetic nerve are not absolutely fixed and constant. According to N. Wedensky the inhibiting effect of the vagus on the heart is due to the fact that excitation of its fibres lowers the lability of the heart and, thus, creates the conditions for parabiotic inhibition (Chapter 50). N. Wedensky found that under certain conditions stimulation of the vagus intensified rather than inhibited the work of the heart. Subsequent data have shown that the direct-current anode, i.e., the agent that lowers excitability, removes the inhibiting effect of the vagus on the heart, while the cathode (negative pole) intensifies this inhibition (I. Arshavsky).

Reflex Influences on the Heart from Various Receptors

Excitation of the vagal and sympathetic centres, i.e., their tone, is determined by reflex mechanisms and varies with the stimulation of different receptors. The reflex regulation of cardiac activity always occurs together with the reflex regulation of the vascular tone (Chapter 16) and is included in the various complex-reflex acts of the organism.

Reflex influences on cardiac activity from the interoceptors. Stimulation of any interoceptors may reflexly alter the activity of the heart. The impulses arising in the interoceptors of the aortic arch and the region of the division of the common carotid artery are especially important among the reflex influences on the heart (Fig. 62). Here there are many vascular baroreceptors,* i.e., receptors of the group of mechanoreceptors stimulated by a rise in the blood pressure in the vessels. The impulses of excitation arising in the given receptors are transmitted to the medulla oblongata. Excitation of the vagal centre and the concomitant inhibition of the centre of the sympathetic nerves of the heart is a reflex response to these impulses. *The higher the arterial blood pressure, everything else being equal, the more intensive the reflex excitation of the centre of the cardiac fibres of the vagus and, consequently, the inhibition of cardiac activity.*

The receptors of the aortic arch and of the carotid sinuses are stimulated by the ordinary arterial blood pressure developed in each cardiac systole; these receptors are also slightly stimulated by the arterial pressure during diastole (p. 162). It follows that the central nervous system constantly receives impulses from the baroreceptors of the carotid sinuses and the aortic arch, which impulses reflexly stimulate the centre of the vagus; this leads to permanent reflex excitation of the centre of the vagal neurons, which inhibit the heart, and is referred to as the vagal tone.

Reflex excitation of the vagal centre (with the concomitant inhibition of the centre of the sympathetic nerves of the heart) in response to the impulses from the baroreceptors of the aortic arch and the carotid sinus is not always constant. Thus, for example, during muscular work, when arterial blood pressure usually rises, this rise in pressure does not reflexly inhibit the heart rate. Nor is any slowing down in the rhythm of cardiac contractions observed in hypertension though in this case arterial blood pressure is maintained on a high level for a long time.

The reflex caused by stimulation of the receptors at the mouth of the venae cavae (the Bainbridge reflex) plays an important part in the regulation of cardiac activity. It occurs in response to a rise in blood pressure in the venae cavae which leads to stimulation of the baroreceptors located in the walls of the venae cavae where they empty into the heart. Afferent fibres from these receptors enter the spinal cord and their excitation reflexly lowers vagal tone and increases the tone of the sympathetic innervation of the heart. In this case the heart rate and the force of cardiac contractions increase.

There are interoceptors in all blood vessels and in all tissues and organs; in addition to baroreceptors there is a mass of chemoreceptors which are stimulated by various chemical agents produced in the process of metabolism. Sufficiently strong stimulation of any interoceptors may lead to reflex changes in cardiac activity.

Cardiac activity is usually inhibited when the receptors of the peritoneum are stimulated. This explains the reflex arrest of the heart easily demonstrated in the experiment on the frog by percussion of the abdomen (Goltz's experiment). The heart sometimes stops reflexly also in man (the arrest is usually reversible) from a strong blow on the abdomen (for example, a knock-out abdominal blow in boxing).

A slowing down and a decrease in the force of the heart-beats are also observed in a number of pathological processes in the abdominal cavity, as well as during considerable stimulation of the receptors of the thoracic cavity and the mediastinum, which occurs when the thorax is opened and during surgical operations on the organs of the thoracic cavity (for this reason surgeons now perform such operations by first barring the spread of impulses along the vagus by novocain).

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* Baroreceptors are sometimes referred to as pressoreceptors.

The activity of the heart may also be altered by stimulation of the receptors of the heart itself. According to a number of authors there are receptors under the endocardium of the left ventricle, whose functional role is analogous to that of the receptors in the aortic arch. Their stimulation occurs during systole when there is a sharp rise in the pressure of the blood which fills the ventricles and reflexly leads to a slowing down of the rhythm of the heart-beats owing to an increase in excitation of the vagal centre. The excitation which arises in the central nervous system during stimulation of these cardiac receptors (and during stimulation of the baroreceptors of the large vessels) does not produce any particular sensations in man (see Chapter 64). In like manner the data furnished by surgeons, who not infrequently operate on the heart under local thoracic anaesthesia, show that during mechanical stimulation of the exposed heart the patient experiences no particular sensations. At the same time certain pathological processes in the heart, especially those connected with insufficient blood supply to the heart muscle frequently produce acute pain; such are the pain attacks observed during constriction of the coronary vessels or during coronary thrombosis. These pain sensations are probably due to stimulation of the afferent endings of the nerve fibres which run from the heart through the stellate ganglion together with the sympathetic fibres and together with them enter the spinal cord on the level of the *I*, *II* and *III* thoracic segments of the latter. Injection of an anaesthetic into this ganglion often relieves these cardiac pains. Heart pains are not localized precisely in the region of the heart (behind the sternum) but are radiated—pain is usually felt in the left shoulder and in the left arm.

Stimulation of the receptors of the heart, which leads to pain sensations, strongly affects the rhythm of cardiac contractions.

The pericardium, as well as the wall of the heart and the epicardium which covers it, contain numerous receptors stimulated, for example, during the production of exudate in the pericardium and during mechanical stimulation of the surface of the heart applied under conditions of a chronic experiment through a fistular tube fastened in the pericardium and in the wall of the thoracic cavity (P. Goncharov). Stimulation of the receptors of the pericardium, when air or a saline solution are introduced into its cavity, leads to a protracted inhibition of the heart-beats; the inhibition is eliminated by suppressing the function of the vagi. The pericardium also contains chemoreceptors. It is possible that the mechanoreceptors of the heart and the pericardium are stimulated in each systole.

A rise in the blood pressure of the pulmonary vessels may reflexly weaken cardiac activity.

The agents, whose action constantly coincides with the stimulation of the interoceptors which reflexly alters the activity of the heart, become conditioned stimuli and, owing to the development of conditioned reflexes, begin to exert the same influence on the heart as the direct stimulation of these interoceptors.

Reflex influences on the heart from the exteroceptors. Stimulation of various exteroceptors, particularly those subjected to traumatic stimulation, most frequently lead to an acceleration of the heart rate (the influence of this stimulation on the force of cardiac contractions is not sufficiently clear). Very vigorous traumatic stimulation, especially if it is prolonged, may lead to a slowing down and a weakening of the heart-beats.

Inhibition of the heart-beats produced by reflex excitation of the vagal centre is often observed when the receptors of the mucosa of the nasopharynx and of the respiratory passages are stimulated, for example, in the initial phase of ether anaesthesia and in inhaling vapours of ammonia and other irritating gases. A diagnostically important reflex on the heart is the reflex increase in excitation of the fibres of the vagus which inhibit the heart in response to finger pressure applied to the eyeball that causes no pain. A greater slowing down of the pulse resulting from the same pressure on the eyeball testifies to a higher excitability of the central structures of the vagus or to a greater sensitivity of the heart to the impulses from this nerve.

Stimulation of the mechano- and chemoreceptors (stimulated during contractions of the skeletal muscles) reflexly increases the activity of the heart and alters the vascular tone. This is why passive flexion and extension of the extremities which stimulate the muscle receptors lead to reflex acceleration of the heart; the latter does not occur if the afferent fibres connecting these receptors with the central nervous system are cut.

Effect of the Blood-Borne Chemical Substances on the Heart

In addition to direct nervous influences the heart is also influenced by various chemical substances, which are carried by the blood, the so-called humoral factors (hormones, etc.). The nervous and humoral influences on the heart are closely related. This relation is primarily due to the fact that the hormones and the other substances which alter the activity of the heart enter the blood as a result of reflex acts, i.e., in response to the stimulation of some particular receptors. Thus, the adrenals secrete adrenalin, which influences the activity of the heart reflexly in response, for example, to the stimulation of the pain receptors. Various changes in the composition of the blood may in their turn stimulate the chemoreceptors which again reflexly influence the tone of the neurons innervating the heart. For example, stimulation of the chemoreceptors of the large arteries during deoxidation of the blood leads to an increase in the activity of the heart owing to reflex excitation of the sympathetic neurons, which accelerate and intensify cardiac contractions, and to reflex inhibition of the vagal centre.

Of the compounds which circulate in the blood and influence the activity of the heart certain hormones, especially adrenalin and thyroxin, are of essential importance. Adrenalin, the hormone produced by the medulla of the adrenals, acts on all organs innervated by sympathetic nerve fibres, and in particular on the heart, as does excitation of the sympathetic nerve fibres. This parallelism is due to the fact that excitation of the postganglionic sympathetic nerve fibres leads to the liberation at their endings of a substance resembling adrenalin, which acts like the latter on the heart muscle by accelerating the heart rate and increasing the force of the heart-beats.

With the body at rest the medulla of the adrenals secrets but little adrenalin which circulating in the blood exerts no essential influence on the activity of the heart. Large amounts of adrenalin enter the blood from the adrenals during considerable muscular work, during hypoxia and during the action of agents which are their signals. This also occurs during so-called emotional stress (for example, in keen pain and during the action of the signals of pain stimuli). In these cases the liberation of adrenalin, like the simultaneous reflex excitation of the sympathetic nerve fibres which innervate the heart, leads to an increase in the work of the heart.

Of the compounds which act on the heart humorally mention should also be made of calcium and potassium ions. An increase in the concentration of calcium salts in the medium which bathes the heart acts as does excitation of the sympathetic nerve, whereas the action of the potassium salts is similar to the action resulting from excitation of the vagus. In lesions of the adrenal cortex, in extensive haemolysis, for example, after transfusion of incompatible blood, after burns and during the late phases of disorders of the renal function (anuria) the concentration of potassium in the blood may increase to such an extent as to impair the activity of the heart.

Influence of the Cerebral Cortex on the Activity of the Heart

Observations dating from hoary antiquity show that the activity of the heart changes under the influence of a number of agents which affect the functions of the cerebral cortex and produce states in everyday life referred to as agitation, pain, fear, joy, anxiety, impatience, etc., or, generally speaking, the *emotions*. Pavlov also mentions this by saying: "... you know a lot of ordinary human sensations which are usually ascribed to the heart.... The heart 'leaps with joy,' the heart 'beats with love,' the heart 'thumps with fear,' the heart 'was wrung with compassion,' etc."*

Pavlov explained such changes in the heart rate as a reaction which in its origin was connected with the reflex changes in cardiac activity during hard muscular work. In animals increased muscular activity and the increased work of the heart connected with it are due to the action of agents which produce hunger, sexual and defensive reflexes. By evoking considerable muscular activity all such stimuli, as well as their signals, lead to an intensification and acceleration of the heart-beats. In man the motor reactions in response to such stimuli (for example, pain) are frequently inhibited. However, man has retained one of the components of motor excitation caused by such agents—acceleration and intensification of cardiac activity. All the signals of stimulations which accelerate the heart rate, including verbal stimuli in man (see Chapter 65), are also connected with the reflex changes in the activity of the heart. This explains the strong influence of verbal stimuli on cardiac activity (and on the functions of the internal organs in general).

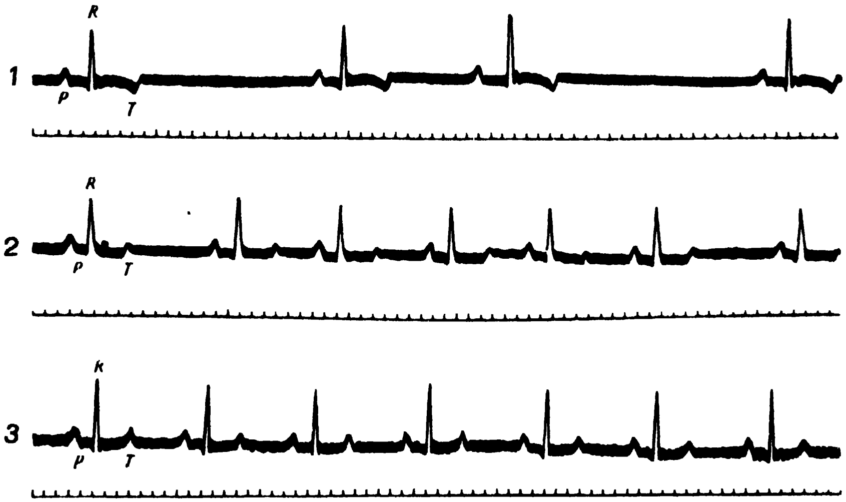

Fig. 40. Conditioned reflex causes changes in cardiac activity.

1 normal electrocardiogram of the dog; *2* - electrocardiogram recorded immediately after stimulation of gastric mucosa by induction current (stimulating electrodes were inserted into stomach through fistula) with stimulation always preceded by beats of metronome; *3* electrocardiogram recorded while only sounds of the metronome were used after they had been combined with stimulation of gastric mucosa 60 times (after Y. Petrova).

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* I. Pavlov, *Complete Works*, Vol. V, p. 330 (Lectures on the Physiology of Circulation).

The influence of the cerebral cortex on the activity of the heart is a result of the development of various conditioned reflexes to cardiac activity A. Ivanov-Smolensky's associates have found that the words which signalize some action capable of changing the activity of the heart produce the same changes in the heart rate as this action itself. V. Delov has shown that any indifferent agent (in relation to the activity of the heart) repeatedly used (30 to 60 times) before a drug, which in some definite manner changes the work of the heart, is injected into the blood, begins to change cardiac activity very much like the drug itself. For example, a tone of a certain pitch repeatedly used at the time strophanthin was injected slowed down the heart rate and changed the conductivity of the heart like strophanthin itself. The situation under which a substance slowing down the heart, for example, morphine, is injected produces the same changes in the activity of the heart as does this substance. The signal of injection of nitroglycerin, a vasodilating substance, leads to the same acceleration of the heart as the injection of this compound. The resulting conditioned reflex is so strong that the use of the conditioned stimulus which accelerates the heart removes the opposite effect produced by subcutaneously injected morphine. Conditioned reflexes affecting the activity of the heart are also developed in response to agents whose influence is connected in time with stimulation of the receptors of internal organs which reflexly alter cardiac activity (for example, with stimulation of the stomach [Fig. 14], the gallbladder or the heart itself).

CHAPTER 14

WORK OF THE HEART UNDER VARIOUS CONDITIONS OF VITAL BODILY ACTIVITY

The activity of the heart is always determined by the conditions under which the body lives. It goes without saying that the properties of the heart itself—the development of its musculature, the excitability and conductivity—also determine the nature of cardiac activity. However, these properties of the heart have formed on the basis of all the preceding conditions of bodily activity and as a result of the influences reflexly exerted on the heart. Such factors, for example, as certain muscular work done repeatedly and the action of a number of poisons and toxins, considerably alter the properties of the heart. At the same time the reaction of the circulatory system to the impulses from various receptors varies with the conditioned reflexes developed in the course of life and influencing the circulatory system (for example, the report of a gun may greatly increase the heart rate in people who seldom hear it while hardly affecting the heart rate of artillerymen). Hence, the reaction of the heart to various influences of the internal and external environments varies in different individuals and in the same individual under different conditions and at different periods of his life.

Heart Rate (Pulse Rate)

The heart rate, usually determined as the pulse rate, depends on all the conditions of bodily vital activity and increases under all conditions which increase the metabolism and the energy exchange in the body.

The heart rate is lowest during deep sleep when the skeletal musculature is almost fully relaxed and the function of the digestive apparatus is reduced. During sleep it normally varies between 50 and 60 per minute. For practical purposes, however, the heart rate is normally taken at complete muscular rest (in a horizontal position no sooner than 10 to 30 minutes after walking or other light work*) several hours after eating and excluding any and all stimuli to the cerebral cortex. Under these conditions it usually varies between 60 and 70 per minute. In children it is always higher under the same conditions of rest than in adults because of their low vagal tone.

The heart rate of less than 60 per minute is designated as *bradycardia* and that of more than 85 to 90 per minute is termed *tachycardia*. Bradycardia is mostly conditioned by an increase in the tone of the vagal centres (for example, in certain cerebral diseases and in abnormally high intracranial pressure). As a normal phenomenon bradycardia is encountered in highly-trained athletes who during complete muscular rest show a pulse rate of 36 to 45. Tachycardia is nearly always conditioned mainly by a decrease in the inhibiting influences of the vagus on the heart. This combines with the influence of the high tone of the cardiac accelerators.

The heart rate is usually irregular even under strictly constant conditions and at complete rest. During inspiration it slightly increases due to the fact that the distension of the lungs and the increase of the blood flow along the veins the the heart reflexly depress vagal tone. During expiration the heart rate somewhat decreases compared with inspiration. These variations in the pulse rate connected with respiration are called *respiratory arhythmia*, particularly pronounced in children.

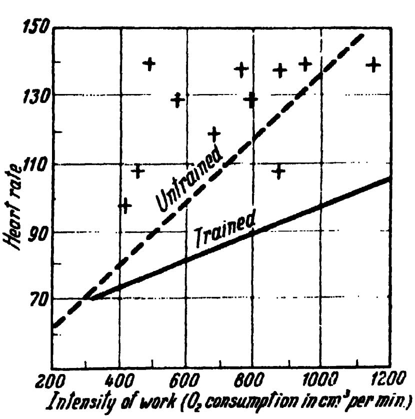

Fig. 41. Heart rate (along ordinate) in trained and untrained subjects. Crosses mark results of individual observations of untrained subjects during muscular work of various intensity corresponding to various rates of oxygen consumption marked on abscissa (after Krogh and Linhard).

Acceleration of the pulse due to lowering of the tone of the vagal centre and a rise in the tone of the accelerators of the heart occurs during muscular work, under so-called emotional stresses and, to a lesser extent, during hard mental work and during increased activity of the digestive tract. The pulse of people trained for muscular activity quickens less than that of untrained people even during the performance of the *same* work (Fig. 41). But if the muscular work is the maximal for the given person (for example, running for a period of 2 to 5 minutes at the highest speed) the *maximal* heart rate is the higher the better his muscular training. In highly trained athletes the pulse rate may rise to 260, whereas in untrained people it never exceeds 200 (Farfel).

Increases in the heart rate are always observed during rises in body temperature.

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* After very hard muscular work the pulse rate often returns to normal for the given subject only within several hours.

Systolic and Minute Volumes of the Heart

The amount of blood pumped out by each ventricle (separately) is called the systolic (or beat) volume of the heart; multiplied by the number of beats per minute it gives the minute volume of the heart. There are indirect methods of determining the minute volume of the heart based on the fact that all the blood pumped out by the right heart goes through the lungs. Let us assume that in one minute man exhales 200 ml. of carbon dioxide with the expired air. If the arterial blood contains 50 volumes per 100 ml. of blood (50 volume $^0/_0$) and if the venous blood flowing from the right heart to the lungs contains 55 volume $^0/_0$, then each 100 ml. of blood gives off 5 ml. of carbon dioxide in the lungs (200 : 5) × 100 ml., i.e.,

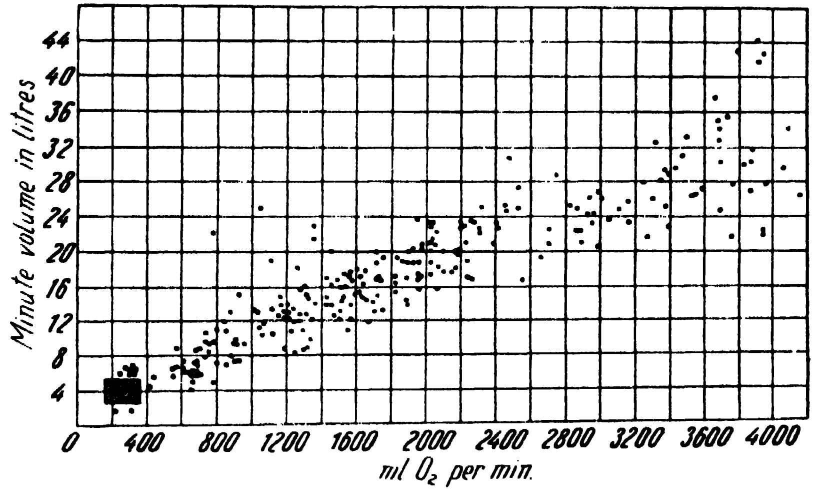

Fig. 42. Minute volume of heart at rest and during work of various intensity. Shaded rectangle shows minute volume in different subjects at rest; data obtained during muscular work are indicated by dots; each dot shows minute volume of each individual person at muscular work done and rate of oxygen consumption (abscissa) (data of several investigators). The diagram shows that the more intensive the work (the more oxygen consumed during its performance) the greater the minute volume of the heart as shown on the ordinate (after Hansen).

4 litres of blood must flow through the lungs per minute which will be the minute volume of the heart. The systolic volume at a heart rate of 80 will be 4 lit. : 80, i.e., 50 ml.

This method of determining the minute volume of the blood proposed by Fick requires a rather complicated estimation of the content of carbon dioxide in mixed venous blood which comes to the right heart from the entire body (p. 203), i.e., the blood of the right ventricle or the pulmonary artery.

Another method determines the minute volume of the heart by the amount of a gas with a precisely known solubility coefficient dissolved in the blood, for example, acetylene added to the inspired air.

The average minute volume of the heart in a healthy adult in a state of complete rest and on an empty stomach varies between 3.5 and 5.5 litres, i.e., approximately 2.2 litres per 1 m.^{2} of body surface (see determination of the latter value above). The normal systolic volume is usually 50 to 80 ml.

After eating the minute and systolic volumes increase by 15 to 20 per cent. During hard muscular work 15 *to 25 litres of blood is pumped out into the aorta per minute; in highly-trained athletes this figure reaches even 40 litres during maximal effort.* Moreover, in people trained for muscular activity the minute volume increases because of a considerable rise in the systolic volume, while in untrained people this increase is due mainly to acceleration of the heart rate. High figures of systolic volume (about 90 to 110 ml.) with a correspondingly slow pulse are noted in physically trained people even at rest, while during hard work their beat volume rises to 150 and even 180 or 200 ml.

Value of Cardiac Work

Mechanical work is measured by the product of the load (in kilograms) multiplied by the height (in metres) to which the load is raised. The value of the mass of blood pumped by the heart from the veins into the arteries may be represented as lifting a load to a certain height. This height corresponds to the blood pressure in the aorta. Let us assume that we have opened the aorta and the blood has begun to spurt upward. The work of the heart then equals the product of the weight of the blood by the height reached by the fountain. This blood pressure which so vividly manifests itself when the blood gushes upward from an open artery acts on the walls of unopened vessels from inside. The blood pressure produced by the work of the heart is expressed in mm. Hg and is easily measured by the methods indicated in Chapter 15. In order to pass on to the height to which the blood pumped out by the heart rises from the value of the blood pressure, we must multiply the value of the blood pressure expressed in mm. Hg by the specific gravity of mercury, i.e., by 13.6 (we can disregard the very small difference in the specific gravity of water and blood).

Hence, the work of the left heart equals QH, where Q is the weight in kilograms or, what is practically the same, the number of litres of blood pumped out by the heart into the aorta, and H is the mean blood pressure in the aorta. Let us assume for the sake of simplicity that the mean pressure equals half the value of arterial blood pressure during systole and diastole. This value is normally close to 100 mm. Hg (0.1 m.), while the amount of the blood driven by the heart into the aorta varies between 3.5 and 5.5 litres per minute at rest and rises to 20 to 30 litres during hard muscular work.

In order to compute the work of the whole heart we must add to the work done by the left ventricle the work of its right half which, owing to the lesser blood pressure in the pulmonary artery compared with the pressure in the aorta, equals 1/4 to 1/16 of the work of the left ventricle. It follows that the work of the heart (not counting the acceleration imparted to the blood) equals $5/4\ QH$ (1/4 is added for the work of the right ventricle). With a minute volume of 5 litres and a mean pressure of 100 mm. Hg in the aorta the value of the work of the heart equals $5/4\ (5 \times 0.1 \times 13.6)$, i.e., 8.5 kg./m. per minute, or in round figures 500 kg./m. per hour and 12,000 kg./m. per day. Since the amount of blood pumped by the heart increases during muscular activity the work done by the heart may reach 1,000 to 2,000 kg./m. per hour (and with a minute volume of 30 litres even 3,000 kg./m. per hour). Considering that man is usually in a state of relative muscular rest no more than 10 to 12 hours per day we must estimate the daily work of the heart at approximately 15,000 to 20,000 kg./m. The lower of these figures corresponds to the work done by a person weighing 70 kg. who climbs 10 times to the fifth floor. In hard muscular work the heart does 30,000 kg./m. of work per day. These values of cardiac work (10,000 to 30,000 kg./m.) with (p. 361) approximately 20 per cent cardiac efficiency are equivalent to an energy output of 120 to 360 large calories. The liberation of such amounts of energy requires a daily consumption of 30 to 90 gr. of carbohydrates or proteins by the heart.

In disorders of cardiac activity characterized by an impairment of the pumping function of the heart there may be a temporary discrepancy between the amounts of blood flowing to and from the heart. If the function of the right heart is impaired the right ventricle does not pump all of the blood coming from the systemic circuit and there is venous congestion—the liver is overfilled with blood, the cervical veins swell up and the pressure in the veins of the systemic circulation rises. If the activity of the left ventricle is inadequate it does not pump all the blood it receives from the veins of the pulmonary circulation into the arteries of the systemic circuit. In this case there is pulmonary congestion with concomitant dyspnoea. The heart is distended in all these cases. The regulatory mechanisms respond by intensifying and accelerating the contractions of the heart which re-establishes the correspondence between the amounts of blood flowing to and from the heart per unit of time.

CHAPTER 15

MOVEMENT OF THE BLOOD ALONG THE VESSELS

Physical Laws Determining the Blood Flow; Blood Pressure and Velocity of the Blood Flow

Let us imagine liquid-filled reservoir *A* (Fig. 43) with a horizontal tube leading away from a permanent section *BD* into which vertical tubes *1*, *2*, *3*, etc., are soldered. By raising the liquid in reservoir *A* to the level *H* we impart to it a certain amount of potential energy measured by the value of the pressure it exerts on the bottom of the reservoir. If the tap at the end of tube *BD* is closed the potential energy accumulated in the reservoir during the rise of the liquid to level *H* is not spent. With the tap closed the water level in the tubes will be equal to that in reservoir *A*. If the tap is open the water runs out of tube *BD* and the water level in tubes *1*, *2*, *3*, etc., drops.

By comparing the water levels in tube *1* and in pressure reservoir *A* we see that the lateral pressure of the liquid in the very beginning of tube *BD* is lower than the water pressure in the pressure reservoir. Consequently, a certain amount of energy expressed by the value $H - h_1 = h_0$ is spent in the very beginning of the system. This energy is spent on imparting a certain velocity to the flow of the liquid. If tube *BD* is very wide so that the velocity of the flow of the liquid approximates the velocity of the fall of a free falling body nearly all the potential energy of the liquid column is changed into the kinetic energy of its outflow and $H - h_1$ approximates H. If the velocity of the flow of the liquid from reservoir *A* is slowed down by friction against the walls of horizontal

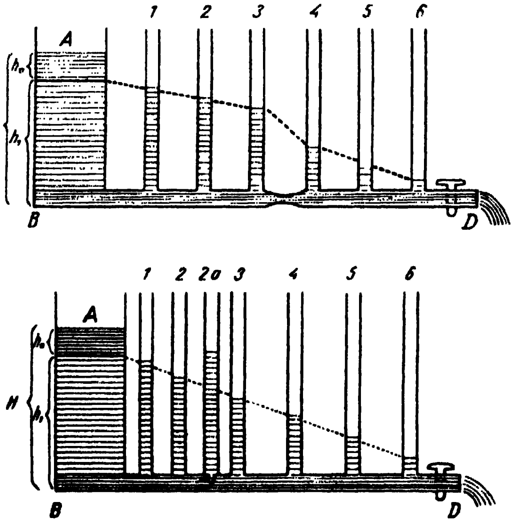

Fig. 43. Diagram illustrating significance of physical factors affecting blood pressure (explanation in text).

tube *BD* it will be the lower the more energy is spent on overcoming the friction of the liquid against the walls of the tube; the value $H-h_1$ decreases (h_0 relatively increases) (compare height of liquid column in tubes *3* and *4*, Fig. 43, top).

Thus, the energy communicated to the moving liquid is spent on imparting a certain velocity to the liquid and on overcoming the friction against the walls of the vessel along which the liquid flows.

In the circulatory system the total amount of energy communicated to the blood by the work of the heart physically corresponds to the potential energy which the liquid had in reservoir *A* of the aforesaid model. The pressure exerted by the flowing blood on the internal surface of the blood vessels is analogous to the lateral pressure of the liquid in tubes 1 to 6 which issue from tube *BD* (Fig. 43).

If we insert a T-tube into the cut ends of a blood vessel and connect its lateral limb to a manometer we determine the pressure of the blood on the wall of the vessel. This pressure expresses the potential energy which the blood still has at the given portion of the circulatory system and which is then spent on overcoming the further resistance to its flow. The energy spent on imparting velocity to the blood is disregarded when the lateral pressure is measured. If we connect with the manometer a tube inserted into the vessel against the blood flow, the blood, beating against the surface of the manometer, which registers the pressure, stops. The final pressure thus recorded indicates not only the potential energy of the blood at the given point of the system, but also the energy spent on imparting a certain velocity to the blood. The lower diagram in Fig. 43 illustrates this by the level of the pressure in tube *2a*, the end of which is directed against the flow of the liquid, and the energy of the velocity of the liquid is, therefore, communicated to the liquid in tube *2a*; the pressure in this tube is higher than the lateral pressure by the height $h_0 = H - h_1$.

Karl Ludwig

In the vascular system the amount of energy spent on imparting velocity to the blood is very small compared with the potential energy communicated to it; the final pressure, therefore, approximates the lateral pressure. Usually when speaking of the value of blood pressure we are not concerned with whether this value includes the kinetic factor of the work of the heart (imparting velocity to the blood) or it is only a question of lateral pressure exerted by the flowing blood on the wall of the vessel.

Since the blood returning to the heart enters its cavity from the veins at some speed the entering mass of blood naturally has a certain energy, but this energy is not utilized when the blood is subsequently pumped by the heart into the arteries because upon entering the heart the blood strikes the walls of its cavities and stops, creating turbulent movements.

The exact measure of the total potential energy communicated by the work of the heart to a unit of blood volume is, consequently, the value of the blood pressure in the initial portion of the aorta. The pressure in all the large arteries, such as the carotid, the brachial, the radial and the femoral, is only a little lower (2 to 10 mm. Hg) than in the aorta. This is due to the fact that in flowing through the large arteries where the resistance is very weak the blood hardly spends any of the potential energy imparted to it by the heart. The easily determined (p. 137) blood pressure in any large artery—*arterial blood pressure* may, therefore, be considered the measure of the potential energy of the blood pumped by the heart into the aorta.

The pressure of the blood in any vessel, including the arteries, is the pressure which the particles of the fluid exert on each other. In a liquid the pressure is evenly exerted in all directions and the pressure of the blood is, therefore, fully exerted on the wall of the vessel along which it flows. The value of the arterial pressure is vividly demonstrated by the height to which the blood spurts from a small wound in the wall of an artery. If we insert into a large artery a tube connected with a vertical glass tube, as it was done by Hales when he measured the arterial pressure for the first time (18th century), the blood in the glass tube will rise 150 to 200 cm. above the body surface of the animal. During each systole the blood rises about 20 to 40 cm. above the level to which it drops during the pause between the contractions of the heart. This method of determining the value of the blood pressure is suitable only for physiological demonstrations.

Arterial pressure is usually measured by means of *manometers* (p. 135). The value of arterial pressure is nearly always expressed in millimetres Hg (1 mm. Hg corresponds to 13.6 mm. H_2O).

Resistance to the Blood Flow in the Different Divisions of the Circulatory System

Measurements of the blood pressure in various vessels show that in all large arteries, visible to the naked eye, the pressure is only slightly lower than in the aorta. This is due to the fact that the resistance offered to the flow of blood in the large arteries is slight and only a small part of the potential energy communicated to the blood forced out into the aorta is spent on its flow along these arteries; during systole the normal pressure in the aorta reaches 115 to 130 mm. Hg. In the beginning of the arterioles the blood pressure is approximately 70 to 80 mm. Hg. During the passage of the blood through the arterioles the pressure sharply drops and the blood flows into the capillaries under a pressure of only 20 to 30 mm. Hg. Having passed through the capillaries the blood enters small veins under a pressure of 8 to 15 mm. Hg; in the thoracic veins, which drain into the heart, the blood always flows under a pressure lower than atmospheric; the blood pressure here is usually 2 to 6 mm. Hg lower than barometric (since the values of pressure, considered in relation to atmospheric pressure which is taken for zero pressure of the blood as it enters the heart, is not infrequently referred to as negative).

If we take the total value of the resistance offered by the entire vascular system of the systemic circulation for 100* the resistance of the arterial network before the blood enters the arterioles will constitute approximately 20 per cent of this value, that of the entire venous system will be about 10 per cent, and that offered by the arterioles and capillaries will amount to about 70 per cent of the total resistance of the entire blood stream. About 3/4 of this value is due to the friction of the blood against the walls of the arterioles and 1/4 to the resistance offered to the blood flow by the capillaries. These values may vary considerably.

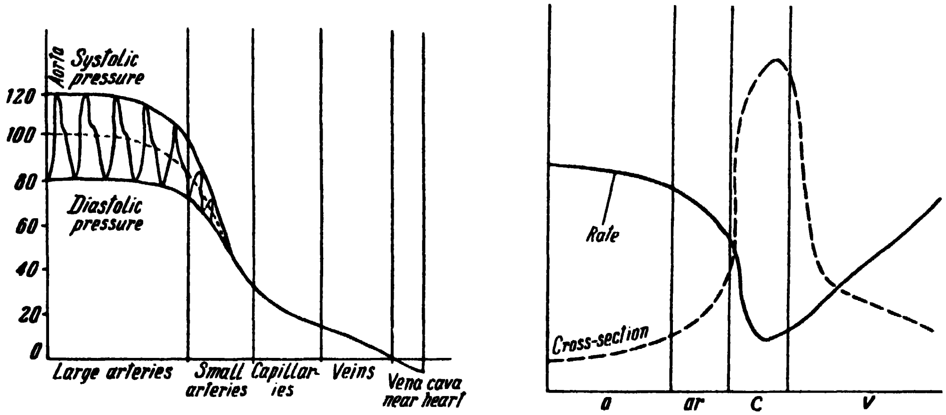

Fig. 44. Left—diagram showing pressure changes in arteries, capillaries and veins; right—diagram showing changes in rate of blood flow and total width of vascular bed in arteries, capillaries and veins.

a— large arteries; ar - arterioles; c capillaries; v veins.

The highest resistance to the blood flow is offered by the arterioles because the summary value of the internal surface of all the arterioles (their summary surface) is dozens of times as great as the summary surface of all the larger arteries while the velocity of the blood flow in the arterioles is still high (it is only 1/2 to 1/3 of the velocity of the blood flow in the aorta, because the summary section of all the arterioles is about three times that of the aorta). The resistance overcome by a liquid in its friction against the walls of vessels is proportional to the square of its velocity. The relatively high velocity of the blood flow in the comparatively long arterioles (whose number is very large) with a very large surface against which the blood rubs is responsible for the fact that the resistance to the blood flow in the arterioles considerably exceeds that in the system of all the large arteries.

The number of capillaries in the body is much larger than the number of arterioles (there are several thousand million capillaries and only several hundred thousand arterioles); the sum of the lumens of all the capillaries is, therefore, about 200 to 400 times that of the summary lumen of all the arterioles and about 800 times as great as the cross-section of the aorta. Owing to this the blood in the capillaries flows very slowly. Since the capillaries are short and the blood flows through them slowly they offer less resistance to the blood flow than do the arterioles.

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* It is clear that the blood overcomes various resistance depending on the course it travels. When we speak of the blood circulation as a whole we mean the summary resistance of the vascular channel offered to the flow of the entire blood pumped by the heart.

The resistance in the pulmonary circulation is 1/5 to 1/6 that of the systemic circulation and the pressure in the pulmonary artery is, therefore, 1/5 to 1/6 of the pressure in the aorta.

Thus, the value of the blood pressure in the vessels is the lower the farther the blood has travelled from the heart and is lowest in the arterioles.

The summary lumen of the vascular bed increases from the aorta to the capillaries where it reaches the greatest value; then it decreases again as the capillaries drain into the veins and the veins merge with other veins (the total lumen of the two venae cavae entering the atrium is slightly larger than the lumen of the aorta). The blood pumped by the heart flows successively through the aorta, all the large arteries, the entire channel of the capillaries and both venae cavae. The velocity of the blood flow is, therefore, the highest in the aorta and the lowest in the capillaries (in the capillaries it is 1/600 to 1/800 that of the aorta). In the veins the velocity of the blood flow increases again and in the venae cavae reaches that of the aortic blood flow. These relations are shown in Fig. 44.

Continuity of the Blood Flow in the Vessels and Significance of the Elasticity of the Arteries

The heart does not pump blood into the aorta and the pulmonary artery continuously, but only during the systoles; during the diastoles no blood enters the arteries from the heart. Despite this the blood flows along the vessels in a continuous stream; its flow does not cease during the diastoles of the heart; moreover, in the arterioles, capillaries and veins far from the heart it always flows at a constant velocity which does not alter during the various phases of cardiac activity. This is due to the elasticity of the arteries and the high resistance to the blood flow in the arterioles.

During ventricular systole the ventricles pump blood into the arteries of the systemic and pulmonary circuits with a considerable speed. Since the resistance to the blood flow greatly increases during the passage of the blood from the arteries into the arterioles the blood cannot be drained from the arteries with the same speed during systole with which it is pumped into them by the heart. The amount of blood contained in the arteries during systole, therefore, increases and the arteries are somewhat distended by this surplus volume of blood flowing into them during systole when the blood is rapidly driven out of the ventricles.

If, for example, 8 ml. of blood flows out of the arteries into the arterioles every 0.1 second, then during systole, which lasts 0.3 seconds, 24 ml. of blood flows out of the arteries. If 40 ml. of blood is driven into the aorta during the first 0.1 sec. of the systole, 20 ml. during the second 0.1 sec. and 10 ml. during the third 0.1 sec. (i.e., a total of 70 ml. during the 0.3 sec.), by the end of the systole the distended arteries will contain 46 ml. more blood than by the end of the diastole (70 — 24 = 46). During the 0.5 to 0.6 sec. of the following diastole these 46 ml. of blood will be flowing through the arterioles into the capillaries and will be moving further along the veins towards the heart.

The distension of an elastic body requires the more energy the less elastic it is. A distended elastic body collapses when the force which distends it ceases to act; the energy spent on distending the elastic body is then liberated. Therefore, when the distension of the arteries by the blood pumped into them ceases in the beginning of the diastole the elastic walls of the arteries, which were distended during the systole, start collapsing. At this time the energy accumulated by the distended arterial walls in the form of potential tensile forces changes into pressure developed by the collapsing arterial walls and transmitted to the blood contained in the arteries.

It follows that the pressure in the large arteries rises during each systole and lowers during each diastole (Fig. 46). The longer the diastole the more the elastic arteries collapse. With the usual duration of diastole the pressure in the arteries does not drop below 40 to 60 mm. Hg, i.e., by the end of diastole the arteries still contain more blood than they could contain with absolutely undistended walls. But if the pause between the systoles is abnormally prolonged (for more than 3 to 5 seconds) the arterial pressure drops to zero.

Thus, during diastole the blood in the arteries flows under the pressure exerted on it by the collapsing elastic walls of the arteries. This creates the continuity of the movement of the blood in the vascular system. No new energy is produced by the walls of the arteries during diastole; what we have is only the release of the energy of the cardiac contraction spent on distending the arteries during systole.

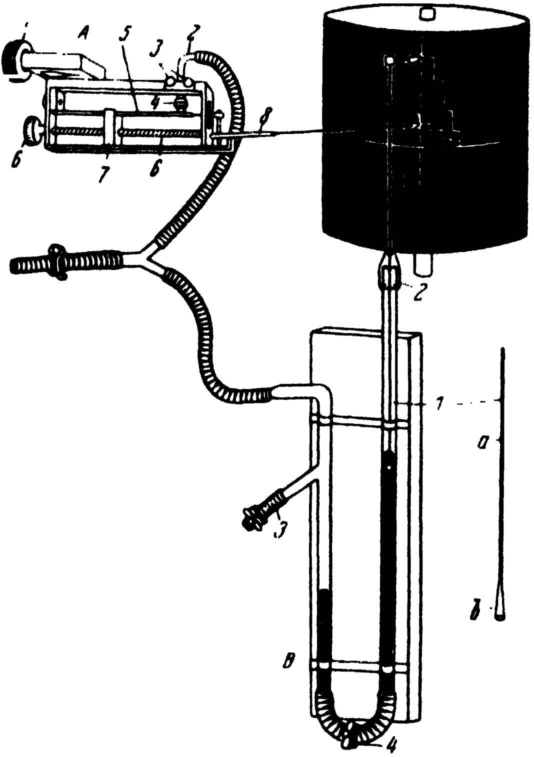


Fig. 45. Ludwig's mercury manometer and Fick's spring manometer (after N. Rozhansky).

A—spring manometer connected with mercury manometer *(B)* for calibrating readings of spring manometer by comparing its deviations with pressure recorded by mercury manometer (recorded on kymograph drum).

Spring manometer: 1—screw on sleeve for tripod; *2*—tube connected with canula inserted into blood vessel. This tube is filled with liquid which prevents blood from coagulating; it ends in small capsule *(3)* held fast by screws; capsule is hermetically sealed with thin membrane. By acting on this membrane through tube blood pressure is transmitted through cone-shaped bone stud *(4)* to flat spring *(5)* connected with lever *(8)* (at zero pressure stud just touches the spring). Tension of spring can be changed by turn of screw *(6)* which moves lug *(7)*.

Mercury manometer: 1—float *(ab)*; *2*—cowl with opening limiting oscillations of float in horizontal plane; *3*—branch piece with clamp making possible filling of manometer tube with solution which prevents blood from coagulating; *4*—screw clamp to stop oscillations of mercury in manometer.

Kymograph drum shows record of mercury pressure and range of lever of membrane manometer being calibrated (after N. Rozhansky).

Measuring Arterial Pressure; Systolic and Diastolic Pressure

Direct methods of measuring blood pressure. Estimation of the blood pressure (especially arterial) is very important in characterizing the circulation of the blood. When the blood pressure is measured directly (in experiments and sometimes in the clinic—puncture of an artery in operations) its value is determined by a manometer connected with a blood vessel. The simplest, very frequently used manometer is a mercury manometer (Fig. 45). A tube (canula), inserted into the cut of an exposed blood vessel, is connected with one of the limbs of a U-shaped manometer by a system of tubes. The entire system of tubes (from the blood to the mercury), is filled with a liquid which prevents the blood from coagulating (for example, a solution saturated with sodium bicarbonate or magnesium sulphate). The difference in the levels of mercury in the two limbs of the manometer shows the value of the blood pressure in millimetres Hg. A pointer fastened to a float on the surface of the mercury records all variations in blood pressure on a paper moved by a kymograph drum.

One of the shortcomings of a mercury manometer is its considerable inertness, owing to which the picture of the variations in the arterial blood pressure is distorted. During brief rises or drops in the pressure the mercury in the manometer has no time to rise or drop to the level of the real pressure. The rapid changes in blood pressure (for example, the variations connected with each cardiac cycle) are, therefore, distorted. The variations in blood pressure are recorded much more accurately by means of manometers which have little inertia, i.e., membrane manometers (Fig. 45 and 48).

Systolic and diastolic, pulse and mean blood pressure in the arteries. During the cardiac cycle the blood pressure in the arteries varies in accordance with definite laws, rising to its maximum in the first half of each systole and lowering to a certain minimum by the end of each diastole. We distinguish correspondingly:

A. *Systolic* or *maximal* blood pressure established in the arteries for a brief period 0.1 to 0.12 sec. after the beginning of systole (the highest point of the curves in Fig. 46). In man's large arteries this pressure normally constitutes 100 to 125 mm. Hg.

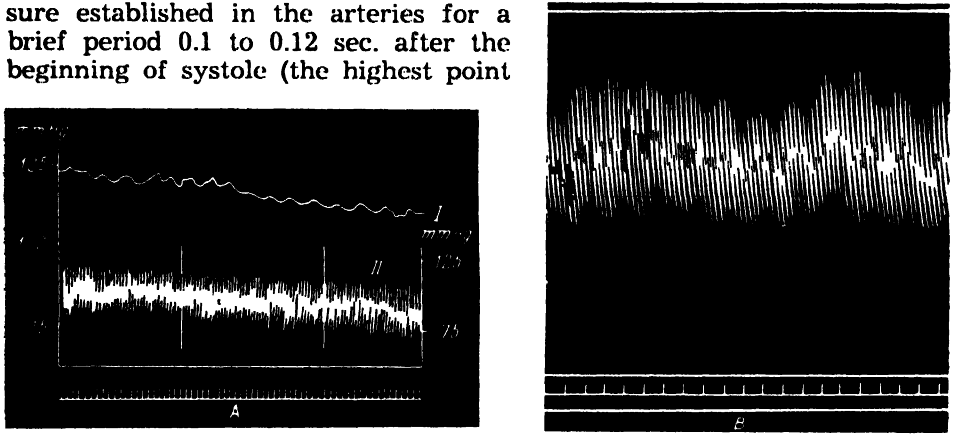


Fig. 46. Curve of variations in arterial blood pressure in the dog's femoral artery. *A* -- record of pressure made by mercury (somewhat muffled) manometer (top) and by spring manometer (bottom) (the scale is on the right). *B* record of arterial pressure by spring manometer (N. Danilov): the record clearly shows cardiac and respiratory variations and waves of third order in arterial pressure. Time intervals 1 second.

B. *Diastolic* or *minimal* blood pressure established towards the very end of diastole (lowest point of the curves in Fig. 46). In man this value is normally between 45 and 80 mm. Hg.

The difference between the values of the systolic and diastolic pressures is designated as the *pulse* pressure. The variations in the systolic and diastolic pressures, equal in magnitude and direction, do not affect the value of the pulse pressure.

Mean pressure. It is possible (as it was first done by I. Sechenov) to connect two limbs of a usual mercury manometer by a rubber tube with a screw clamp. If the tube connecting the two limbs of the manometer is constricted the mercury will pass through the constricted lumen so slowly that the rapid variations in the pressure connected with the cardiac cycle will be suppressed and the manometer will show only the resultant of all the beats acting on the mercury, i.e., it will reflect the mean figure of blood pressure.

On a curve recorded by a manometer of little inertia the value of the mean pressure can be determined as the quotient resulting from the division of the area (in square centimetres), circumscribed by the line of the blood pressure record, by the time (in seconds) during which the pressure was recorded. The dividend is the area circumscribed by the pressure curve above, the zero line below, and on the sides—two perpendiculars dropped to the zero line from two points chosen at random but necessarily similarly located on the curve.

Determination of blood pressure in man. The blood pressure in man is usually measured (by a bloodless method) in the brachial artery. An elastic cuff of a sphygmomanometer enclosed in nonextensible material is placed about the arm. By pumping air into the cuff under control of a manometer we determine the value of external pressure which balances the blood pressure in the compressed (brachial) artery. The pressure in the cuff is transmitted through the skin to the muscles and vessels, which pass through the upper arm, and to the brachial artery, in particular. In order fully to compress the artery we must apply pressure from without equal to the blood pressure in the compressed vessel (plus the pressure needed to overcome the resiliency of the vascular wall and the soft tissues which cover it).

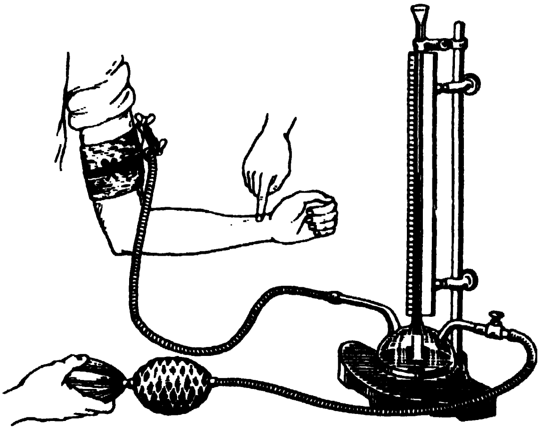


Fig. 47. Sphygmomanometer of Riva-Rocci.

When the brachial artery is fully compressed the pulse waves in the arteries distal to the compressed site of the brachial artery disappear. The disappearance of the radial or ulnar pulse, therefore, corresponds to the moment when the pressure exerted by the cuff on the brachial artery barely exceeds the maximal value of the blood pressure in this vessel. The value of arterial pressure equals the value of the pressure in the cuff placed about the arm under which the pulse waves below the cuff, for example, in the radial artery are no longer palpated.

By opposing the pressure in the cuff, which compresses the arm, to the blood pressure in the artery we measure along with the blood pressure in the vessel also the force of the blood stream plus the pressure required to overcome the resiliency of the arterial wall and the soft tissues of the arm; the local factor—the degree of resiliency of the tissues and arteries at the compressed point—is added to the phenomena which characterize the cardiovascular system as a whole (the value of arterial pressure).

"Korotkov" sounds. Under a certain pressure characteristic sounds are auscultated through the phonendoscope in the artery distal to the portion of the arm compressed by the cuff. These sounds were discovered in 1905 by N. Korotkov at M. Yanovsky's clinic in Petersburg. The sounds now called the Korotkov sounds the world over arise almost suddenly when the pressure in the cuff placed about the arm reaches a value normally between 50 and 70 mm. Hg. With a rise of the pressure in the cuff to about 100 to 120 mm. Hg the sounds suddenly disappear.

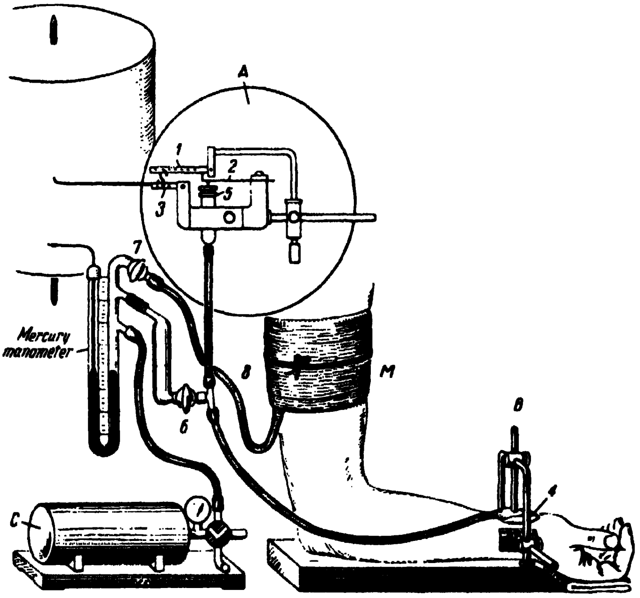


Fig. 48. Graphic determination of maximal and minimal blood pressure in man.

A spring manometer for sphygmogram recording (compared with other parts of illustration manometer is enlarged): *1*—light lever driven by flat spring *(2)*; magnified movements of this lever are recorded on kymograph by lever *(3)*; pulsation of radial artery is transmitted to rubber capsule *(4)* of sphygmograph *(B)* and thence through nonextensible tube to capsule *(5)* of spring manometer. With rise in pressure in cuff *(M)* which compresses brachial artery by air being let into it from balloon *(C)* through tap *(7)* and tube *(8)* characteristic changes in sphygmogram occur. During examination tap *(6)* is closed (after N. Danilov).

In practice when measuring the arterial pressure we use the so-called decompression method. First, we intentionally raise the pressure in the sphygmomanometer cuff to a point higher than systolic and then gradually let the air out of the cuff. The first Korotkov sounds appear the moment the pressure in the cuff drops slightly below systolic; this is due to the fact that at this moment blood begins to penetrate into the distal portion of the artery during systole and distends the arterial walls. When the pressure in the cuff drops slightly below diastolic the pulsations in the arterial wall distal to the cuff sharply decrease. This is probably due to the fact that when the pressure in the cuff drops below diastolic the artery over which the sounds are auscultated during diastole is not empty (the blood penetrates into it under the cuff also during diastole). Thus, the sounds over the ulnar artery disappear when the pressure in the cuff equals diastolic, i.e., minimal.

The maximal and minimal blood pressures in man can also be recorded graphically by registering the pulse waves of the radial artery during the compression of the brachial artery (Fig. 48). The value of the pressure in the sphygmomanometer cuff at which the amplitude of the pulse waves in the radial artery begins to decrease is close to that of the minimal pressure in the brachial artery, whereas the pressure at which the peripheral pulse disappears is close to the maximal arterial pressure (N. Danilov; Figs. 48 and 49).

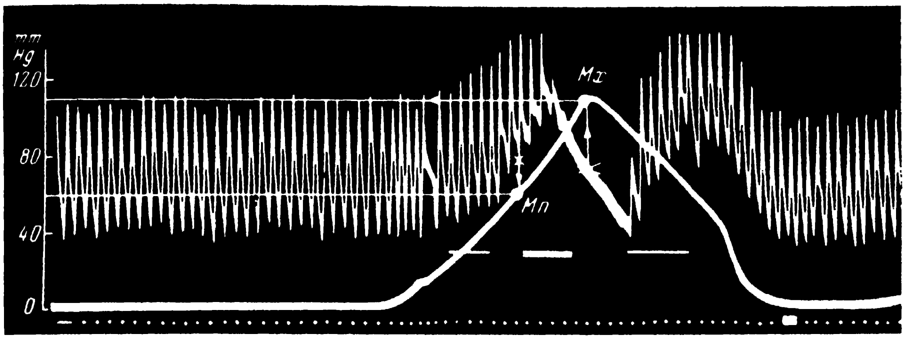


Fig. 49. Determination of systolic and diastolic blood pressure by method illustrated in Fig. 48.

Mn level of diastolic pressure corresponding to pressure in cuff which compresses arm at the time amplitude of pulsations begins to decrease; *Mx* level of systolic pressure (pressure in cuff which causes pulsations recorded by sphygmograph to disappear). Lower heavy line shows pressure in cuff compressing arm. Bottom—time intervals (1 second) (after N. Danilov).

Oscillometric registration of mean pressure in man. When a stream of blood penetrates into the artery compressed by the cuff during systole the pressure in the artery rises. The rise in pressure is, naturally, transmitted from the artery to the cuff. These variations in pressure can be registered as follows (Fig. 50):

The tube running from the cuff is connected with the cavity of the manometer contained in a hermetically sealed case with a glass lid. The cavity of the case is connected with the same tube that runs from the cuff to the manometer. The connecting tube has a tap by which the cavity of the case can be shut off from the cavity of the cuff or the opening of the connecting tube can be constricted or dilated. If the pressure in the case equals that in the capsule of the manometer the latter will show no deflection. But if the cavity of the case is shut off from the cavity of the cuff after the pressure in the cuff rises to, say, 60 mm. Hg (the capsule remains connected with the cuff) the manometer will show all the variations in the pressure above the pressure level in the cavity of the case.

With this method it turns out that the variations in pressure in the cuff, i.e., the beats of the artery become maximal when the pressure in the cuff equals the mean arterial rather than the diastolic pressure, as some investigators believe (Yarotsky, Savitsky). The value of the mean pressure is more constant than the values of the systolic and the diastolic pressures.

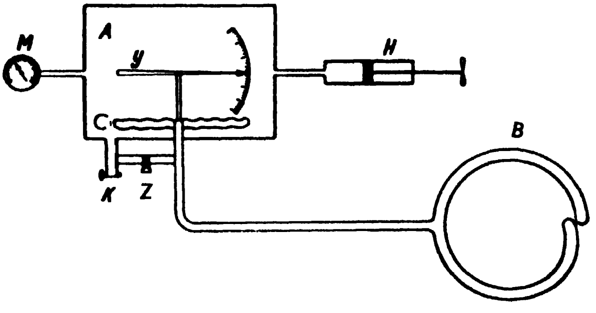


Fig. 50. Pachon's sphygmomanometer for measuring maximal and mean (and by opinion of a number of authors maximal and minimal) pressure in arteries.

B--cuff; *H*- pump for blowing air into system; *A*---chamber surrounding barometric capsule *(C)* whose wall oscillations are transmitted to needle *(Y)* and are recorded on scale of aneroid barometer *(M)* graduated from 0 to 300 mm. Hg; *Z*--clamp by which interior of cuff *(B)* can be disconnected from chamber *(A)* (when clamp is shut all pressure oscillations in cuff are transmitted to capsule); *K* tap for letting air out of the system.

Normal Values of Arterial Pressure in Man

The value of the blood pressure may vary with a number of factors (see below). However, if the blood pressure is measured under strictly constant conditions this value in healthy humans turns out to be constant. During complete physical and mental rest the normal value of the systolic blood pressure in a human being 20 to 40 years old may be taken as 100 to 125 mm. Hg, the diastolic pressure—60 to 75 mm. with a pulse pressure of 35 to 55 mm. The first two values somewhat increase with age, and in people 50 to 60 years old the systolic pressure is usually 120 to 140 mm. As to the diastolic or minimal pressure it either remains unchanged or even drops slightly.

The blood pressure lowers somewhat during sleep; even in the absence of sleep it is lower at night than during the day (diurnal periodicity). Considerable muscular work, as well as any emotional stress, provoke a rise in blood pressure.

The blood pressure in the arteries exerts an essential influence on the blood circulation. The difference between the blood pressures in the beginning of the arterial and at the end of the venous systems depends on the value of the blood pressure in the large arteries, because the blood pressure in the venae cavae at the point of entrance into the right atrium is quite constant. Under normal conditions the absolute value of the blood pressure, therefore, determines the velocity at which the blood flows along the vascular system.

Effect of changes in cardiac activity on arterial blood pressure. Any increase in the amount of blood pumped by the heart into the arteries per unit of time, everything else being equal, leads to a rise in the arterial blood pressure.

If the increase in the minute volume of the heart is due to an increase in the stroke volume the systolic pressure rises somewhat more than the diastolic. If, on the other hand, the increase in the minute volume of the blood pumped into the arteries is a result of a faster heart rate with a lower stroke volume of the heart it is mainly the diastolic pressure that rises because during the shorter period of diastole the pressure in the arteries drops less than during the longer period with a slower heart rate; the pulse pressure also drops somewhat, accordingly.

Since the pressure in the arteries during diastole drops the slower heart rate, everything else being equal, must cause a drop in the diastolic pressure.

Effect of changes in the arteriolar resistance on arterial blood pressure. If the lumen of the vascular system is constricted, which is due primarily to a constriction of the arterioles, but the amount of blood pumped by the heart has not changed, the same amount of blood now flows through the narrower stream as did through the wider stream before. Consequently, the linear rate of movement of the blood through the arterioles increases. Since the expenditure of energy on overcoming friction is proportional to the square of the velocity of the movement of liquid the flow of the blood through the arterioles can be accelerated only by increasing the expenditure of energy. Inasmuch as the energy is communicated to the blood only by the work of the heart it is clear that an increase in the resistance of the arterioles must lead to an increase in the potential energy imparted to the blood by the heart, this increase being responsible for the rise in arterial pressure. This may be accomplished only if in pumping an invariable volume of blood against greater resistance the heart contracts with greater force. Consequently, a constriction of the vessels, especially of the arterioles, everything else being equal, leads to an increase in the arterial pressure.

With a constriction of the arteriolar lumen and a concomitant increase in the resistance to the arteriolar blood flow the diastolic pressure shows a particularly sharp rise. The systolic pressure also rises, however, because an increase in the resistance to the flow of blood in the arterioles leads to an increase in the work of the heart.

The most appreciable changes in arterial resistance are due to alterations in the arteriolar lumen of the abdominal organs and—to a lesser extent—of the skin. A considerable dilatation of the small arteries in the abdominal cavity suffices to cause a sharp drop in the arterial blood pressure (to 50 and less mm. Hg) which cannot be equalized either by an increase in the work of the heart or by a constriction of vessels in other organs. A rise in resistance in the arterioles of the abdominal cavity leads, contrariwise, to a sharp rise in the blood pressure, up to 200 and more mm. Hg. This is explained by the fact that with a dilatation of the arterioles in the abdominal cavity a large amount of blood (up to 3/4 of its total amount) flows into the abdominal organs (into their arterioles, capillaries and veins).

Effect of changes in the amount of blood on the blood pressure. An increase in the amount of blood circulating in the vascular system raises the blood pressure because, everything else being equal, an increase in the mass of blood moved by the heart always leads to an acceleration of its flow and, consequently, to an increase in the resistance to the blood flow. A decrease in the amount of blood circulating in the vascular system, everything else being equal, causes a drop in the blood pressure.

Effect of the size of the lumen of capillaries and veins on arterial blood pressure. The resistance to the blood flow in the capillaries and veins is relatively low compared with that in the arterioles. The effect of the variations in the size of the lumen of these vascular regions on the value of the blood pressure is determined not so much by the ensuing changes in the general resistance to the blood flow as by the altered conditions for the return of the blood to the heart. A considerable dilatation of the vascular channel in the capillaries and veins leads to considerable congestion in them. The flow of blood to the heart decreases and the blood pressure drops as in a decrease in the mass of blood. On the contrary, a constriction of the capillaries and veins over a large body area leads to a flow of the blood away from them into the large veins and thence to the heart. The work of the latter increases and the arterial pressure, everything else being equal, rises until the flow of the blood to the heart decreases to its former value.

Effect of the viscosity of the blood on blood pressure. The more viscous the blood, the higher its friction against the walls of a vessel and, consequently, the greater the resistance offered to its flow in the vessels. Everything else being equal, an increase in the viscosity of the blood must lead to a rise in the arterial blood pressure. The blood becomes more viscous as the amount of erythrocytes per unit of its volume increases. Changes in the viscosity of the blood play a subordinate role among the factors determining the blood pressure because normally the viscosity of the blood does not alter significantly. In certain pathological states the increased viscosity of the blood may be of great importance.

Variations in Arterial Blood Pressure

The curve of the record of arterial blood pressure shows (Figs. 46 and 51) that in addition to the variations in pulse pressure (*waves of the first order*) there are also variations connected with respiration (*waves of the second order*). The blood pressure somewhat rises with each inspiration and drops a little with each expiration. There are several reasons for these respiratory waves on the blood pressure curve: an increased blood flow to the heart during an inspiration, a concomitant acceleration of the heart and also the fact that the stimulation of the respiratory centre (Chapter 22) affects the innervation of the vessels causing a slight constriction of the arterioles.

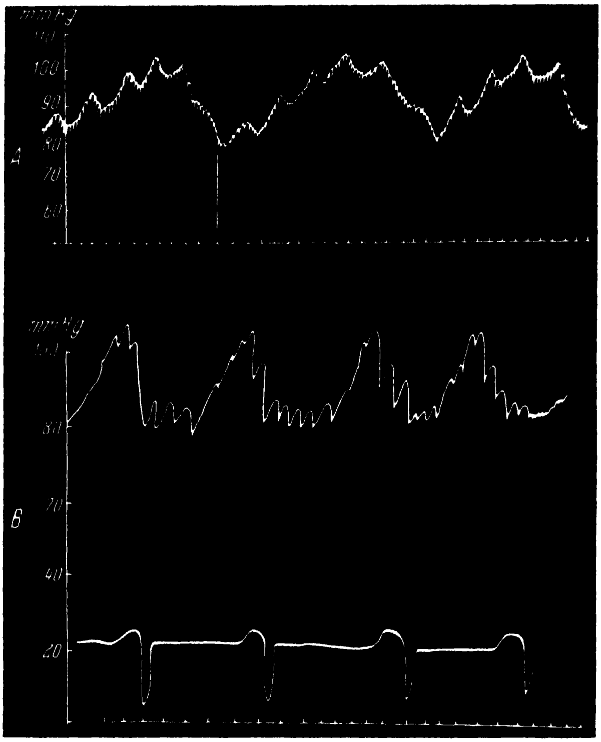


Fig. 51.

A—blood pressure curve (mercury manometer) with pulse waves clearly visible (small and numerous notches), respiratory waves each embracing [illegible]-12 pulse waves, and slow waves (3 waves) of third order unconnected with respiratory movements (after Rozhansky); *B* - blood pressure curve after separating cerebral hemispheres from medulla oblongata and spinal cord. Vagi have been cut. Waves of rising blood pressure preceding abnormally infrequent respiratory movements (lower curve) are shown against background of the latter.

Very large respiratory waves are sometimes noted on the blood pressure curve. Such waves (Traube-Hering curves) are observed during abnormally slow respiration and are conditioned by the rare "explosions" of the strong excitation in the respiratory centre.

The blood pressure curve (see Figs. 46 and 51) not infrequently shows slow waves each taking in a period of several respiratory movements and, consequently, not directly connected with respiration (they are called *waves of the third order* or Meyer's waves). They are, no doubt, dependent on changes in the nervous centres which influence the width of the vascular channel. These waves arise when insufficient blood flows to the cerebrum and during increases in intracranial pressure, but may also be due to functional changes in the cerebral cortex.

Blood Flow and Blood Pressure in the Veins

The blood can flow only from a region of higher pressure to a region of lower pressure. The pressure in the "beginning" of the venous system near the capillaries varies between 80 and 200 mm. H_2O.

The pressure in the veins is measured by the same manometers as in the arteries, but because of the low value of the venous pressure use is ordinarily made of a manometer filled with water rather than mercury. The venous pressure is easily measured in man directly by connecting a manometer through tubes filled with a fluid to a needle inserted through the skin into a superficial vein, usually the ulnar.

A small but still positive pressure in the beginning of the venous system is due to the remainder of the driving force communicated to the blood by the work of the heart and not spent on overcoming friction in the arterioles and capillaries. This force is called *vis a tergo* (*driving force*) and is an important factor in the flow of the blood along the veins.

The second factor, which facilitates the flow of blood to the heart, is the negative pressure in the thoracic cavity exerted on the blood through the thin venous walls and partly through the thin wall of the right atrium. The reasons for this phenomenon will be considered in the study of respiration. Suffice it to say, meanwhile, that the pressure in the veins of the thoracic cavity is 4 to 7 mm. Hg lower than atmospheric during an inspiration and 3 to 5 mm. Hg below atmospheric during an expiration. Because of this the difference in pressures between the beginning of the venous system and the point where the venae cavae enter the heart increases and facilitates the flow of the venous blood to the heart.

The third factor, which influences the flow of blood to the heart, is the activity of the skeletal muscles. Harvey was one of the first to observe that the contractions of skeletal muscles compressed the thin-walled veins running in-between the muscles. Under the circumstances the pressure in the veins rises and, since the venous valves do not let the blood flow towards the capillaries, any local rise in the venous pressure due to compression by the contracting skeletal muscles aids in driving the blood towards the heart (*muscular pump*). However, the skeletal musculature influences the circulation only when the muscular contractions alternate with relaxations because only then do the veins alternately fill and empty. That is why in walking, for example, the conditions for the flow of the blood from the muscles to the heart are much more favourable than in standing.

The pressure exerted by the diaphragm on the abdominal organs in respiration is of certain importance to the venous blood flow. During an inspiration the diaphragm lowers and presses on the organs of the abdominal cavity; at this time the blood is pressed out of the abdominal organs into the region of the portal vein and from the system of the latter into the vena cava.

The drop in the absolute value of the pressure in the veins of the thoracic cavity which occurs during an inspiration also aids in increasing the flow of blood to the heart.

The walls of all the vessels located below the heart when the body is in a vertical position are affected by a hydrostatic factor—the gravity of the blood column. This leads to an accumulation of blood in the vessels located below the heart and to their distension, especially the veins which distend much easier than the arteries. However, the contraction of the musculature of the vascular walls prevents a considerable accumulation of blood in the venous vessels. If the vascular musculature does not regulate the circulation or does it inadequately when the body is in a vertical position large amounts of blood accumulate in the veins of the extremities and of the abdominal cavity.

The veins are extraordinarily easily distended even by a slight increase in the pressure of the blood that fills them. Owing to this the venous system is a reservoir of variable capacity and is able to hold at least 2/3 of the blood found in the body.

Significance of the value of venous pressure. The pressure in the medium caliber veins is normally 60 to 80 mm. H_2O. The constancy of this value is important to normal circulation. A rise in venous pressure (up to 200 to 250 mm. H_2O in the veins of the arm) leads to a rise in the capillary pressure. This creates the conditions for an increased penetration of fluid into the tissues (p. 75) which explains the frequent cases of oedema during rises in venous pressure. Such a rise in venous pressure occurs in certain diseases, for example, in tricuspid insufficiency and in weakened activity of the right ventricle.

Low venous pressure (10 to 30 mm. H_2O) in the region of the medium caliber veins leads to a decrease in the difference of pressures between the capillaries and the right atrium. Owing to this the flow of blood to the heart is impeded with resulting phenomena of venous congestion—overfilling of the veins with blood.

Velocity of Blood Flow

In addition to the blood pressure in the various divisions of the vascular system circulation is also characterized by the velocity of the blood flow. A direct determination of the velocity of the blood flow in the arteries and veins is possible only in an experiment on an animal (Fig. 52 shows the apparatus which first made it possible to take such measurements).

In order to determine the intensity of the blood flow high frequency electric current is passed through a vessel. It is clear that, everything else being equal, the temperature of the blood heated by the current will rise the higher the less blood flows through the vessel. By determining the temperature of the blood in the portion where the current was passed through the vessel it is easy to find out after a required calibration of the apparatus how much blood has flown through the vessel. The temperature of the blood is determined here by the deviations of the galvanometer (thermo-electric method) and these deviations are photographed on sensitized paper moved by a kymograph. A record of the intensity of the blood flow is thus made. The negligible inertia of the apparatus makes it possible to account for the variations in the value of the blood flow during brief periods of time, for example, during the various phases in the cardiac cycle.

It is usually difficult to determine the velocity of the blood flow and the amount of blood flowing through a given vessel (volume velocity of the blood flow); determination of the variations in the volume of an extremity depending on its filling with blood is more frequently used (p. 171).

The velocity of the blood flow in the capillaries can be established by observing in a microscope the velocity of the flow of an individual erythrocyte through a capillary.

Circulation time refers to the time (in seconds) it takes a drop of blood to traverse both the systemic and the pulmonary circuits. This time is determined as follows: a harmless dye or radio-active isotopes are injected into a vein, for example, the ulnar. When the portions of the blood, continuously collected from the same vein on the opposite side, show traces of the injected substance it means that it has travelled together with the blood along the vein from the point of injection to the right heart, traversed the pulmonary circuit, entered the left atrium, covered the entire systemic circuit and reached the same vein on the opposite side.

The total time the blood requires to travel the entire circuit is taken approximately at 25 pulse beats (20 to 25 seconds). With an acceleration of the pulse it decreases correspondingly. It takes the blood approximately 10 to 12 seconds to flow through the pulmonary circuit and the heart (from vein to artery).

Injection of certain substances into the blood is also frequently made use of for determining the rate of the blood flow; by stimulating the receptors located in the region of the division of the carotid artery these substances reflexly cause a change in respiration (a deep inspiration). Here we, consequently, have the interval of time between the injection of lobeline into the blood and the change in respiration which includes the time it took the blood to pass from the ulnar vein to the right heart, the time of its flow through the pulmonary circuit and the time it required to flow from the heart to the division of the carotid artery. Since the blood flows fast through the large veins and arteries this method actually determines mainly the velocity of the blood flow through the pulmonary circuit. The use of this method (Teplov) has shown that it nortakes the blood an average of 12 seconds to the aforesaid distance.

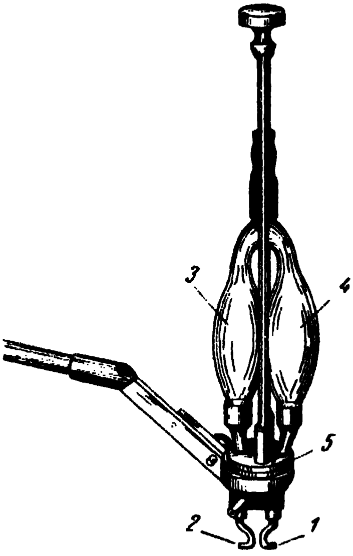


Fig. 52. Ludwig's stromuhr.

Tube 1 is attached to proximal portion of severed artery and tube 2 to its distal portion. In the beginning of experiment vessel 4 is filled with oil and vessel 3 (of the same capacity as vessel 4) with saline. When blood fills vessel 4 the oil contained in it will pass into vessel 3, while saline will be forced from the latter into distal end of artery. When vessel 3 is filled with oil (and vessel 1 with blood) movable frame 5, on which vessels 1 and 3 are fastened, is turned so that vessel 1 is now connected with tube 2 and oil-containing vessel is connected with tube 1. Since we know capacity of vessels and number of times we had to turn frame during definite period we can easily compute amount of blood that has flown through the meter.

Circulation in the Capillaries

Investigating the capillaries. The study of capillaries involves microphysiological investigation of minutest objects. In living tissues we can study the capillaries on the surface of internal organs (kidneys, intestines, mesentery, muscles, brain, etc.) under a microscope. The capillaries of the human skin and in the nail bed are also easy to study; with a strong light it is not hard to discern in the microscope (Fig. 53) the loops of these capillaries (*capillaroscopy*). The study of tissue preparations whose capillaries are filled with a dye is an important method of investigating the capillaries. The preparations are made of tissues that were in various functional states before the moment of fixation (A. Krogh).

Indirect methods are ordinarily employed in determining the value of the capillary blood pressure. For example, a record is made of the load which must be put on a glass plate placed on the nail in order to turn the nail white which will occur when the load slightly exceeds the blood pressure in the capillaries.

Properties of precapillaries and capillaries. The length of each capillary does not exceed 0.2 to 4 mm. and the width, i.e., the diameter of the lumen, about 0.007 mm. Thus, the volume of each capillary is extraordinarily small, measuring millionths of a millilitre; at the rate of the blood flow through them corresponding to about 5 mm. per second (A. Nesterov) it takes 1 mm.^{3} of blood several hours to flow through each capillary. The low rate of the blood flow through each capillary is compensated by their vast numbers (up to 3,000 capillaries per 1 mm.^{3} of active tissue).

The true capillaries, i.e., the vessels whose walls are made of only one layer of endothelial cells, begin from the minutest arterioles called precapillaries. The walls of the precapillaries, i.e., the terminal divisions of the arterioles, still contain a certain number of muscle fibres.

The true capillaries form loops which begin at the precapillaries and enter either other precapillaries or veins. At the point where the capillary arises from the precapillary there is frequently a precapillary sphincter—a circular cluster of smooth-muscle fibres which engird the capillary and are innervated by sympathetic nerve fibres. Contraction of a precapillary sphincter may completely exclude the corresponding capillary from the blood flow.

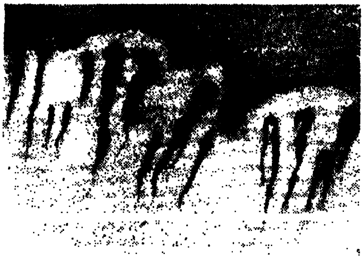


Fig. 53. Capillaries in nail-bed of human finger.

Various nerve endings of efferent fibres have been traced to the precapillary arterioles and to the miniature sphincters encircling the sites where the capillaries arise. Some authors deny the presence of efferent nerve endings in the walls of the capillaries, but the presence in the capillaries of endings of afferent vessels whose other branches terminate in the tissues surrounding the capillaries has been very definitely established (mainly by B. Lavrentyev's associates).

The walls of capillaries are made of endothelial cells and of an intercellular cement substance which fills the entire space between these cells. This substance is constantly renewed by the activity of the endothelial cells of the capillaries, and the permeability of the capillary walls has of late been ascribed precisely to this intercellular connective substance of the capillary wall.

It is logical to assume the existence of direct nervous influences on the permeability of the capillary walls. However, there are no experimental data confirming such influence as yet except the facts which testify to the existence of reflex influences from the intestinal receptors on the permeability of the alveolar septum (p. 197) consisting of the walls of the capillaries of the pulmonary artery and the wall of the pulmonary alveolus.

Contractility of capillaries. The capillaries have the ability to contract owing to which the lumen of the capillary can be entirely occluded (Fig. 54), constricted or dilated. According to Krogh the resting muscle of the guinea-pig has only 100 to 200 open capillaries per 1 mm.^{3}, the others being closed. In a muscle which is in a state of maximal activity the number of open capillaries increases to 3,000 per 1 mm.^{3}, while the summary volume of all the capillaries may reach 10 per cent of the volume of the muscle. In the resting muscle of the frog the distance from one capillary to another is up to 0.8 mm., while in active muscles this distance decreases to 0.06 to 0.1 mm.

It follows that the number of functioning capillaries (along which the blood flows) varies with the state of the tissues these capillaries nourish. The higher the metabolism of a tissue the more open capillaries it has and, consequently, the larger the surface of contact between the tissue (the tissue lymph, to be exact) and the blood.

Most investigators studying this question acknowledge that the capillary walls have the power of independent contractility. It has been demonstrated in a number of cases that the size of the capillary lumen alters independently of the pressure changes in the arterioles which carry blood to these capillaries. Alterations in the capillary lumen may be observed even after tying off the artery which nourishes these capillaries. Besides, the closed capillaries do not open even when the pressure in the arteries is artificially raised 50 mm. above normal. We must, therefore, assume that the capillary wall may relax independently of the value of the blood pressure under the influence of as yet unknown factors.

Some investigators believe that the capillaries close because of the contraction of the adventitious cells, the so-called *Rouget cells,* located in the outer wall of some portions of the capillaries; it is more probable, however, that by contracting or swelling up the endothelial cells may alter the capillary lumen and that the contraction and relaxation of the precapillary sphincters also play an essential part in the opening and closing of the capillaries.

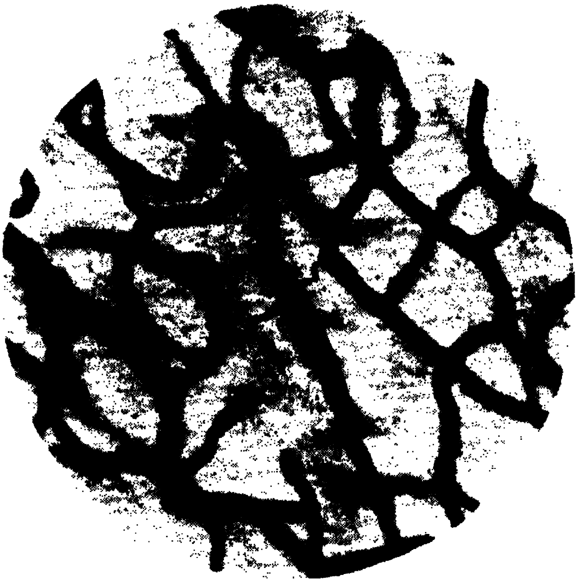


Fig. 54. Capillaries in cerebral cortex. Closed capillary seen in centre (after B. Klosovsky).

The precapillaries are alternately rhythmically constricted and dilated, being mostly constricted in resting tissues. As the tissue metabolism increases the periods of the precapillary dilatation grow longer and the precapillary sphincters, until then closed, open. The regulation of these processes requires further study.

Blood Depots

Not all the blood of the vascular system equally participates in circulation. Let us examine Fig. 55. The top shows a lateral cul-de-sac, capable of considerable distention, arising from the blood vessel. It is clear that if the wall of this sack relaxes the sack will become distended and its cavity will hold a considerable amount of blood. This blood will be stored away, as it were, and will not take part in the circulation until a contraction of the wall of this storehouse brings the blood out into one of the vascular thoroughfares.

The spleen as a blood depot. The vascular system of the spleen resembles the aforesaid system; S. Botkin, the first to describe this system, showed that considerable congestion may occur in it. Barcroft showed that 10 to 20 per cent of the dog's blood may be stored in its spleen (in man, appar-

ently, somewhat less—8 to 12 per cent). Such overfilling with blood leads to a considerable increase in the size of the spleen. If the spleen of the animal is brought out under the skin or through a cut in the skin to the exterior the changes in the size of the spleen can be measured.

When the smooth musculature of the spleen is relaxed the blood stays in its distended vessels—lacunae, but when it contracts the blood is forced out into the general bloodstream. The muscles of the spleen contract reflexly in pain, muscular work, oxygen insufficiency and at high temperature. Various agents coinciding in time with muscular work and pain cause the spleen to contract because of the development of conditioned reflexes (Bykov).

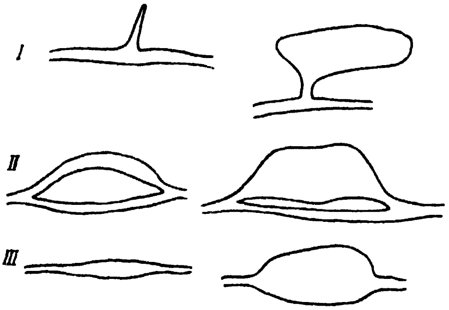


Fig. 55. Diagram of three depots.

In the spleen the functions of a blood depot are most clearly pronounced because the blood accumulated in its vessels is practically completely excluded from the circulation; the blood deposited here mixes with the circulating blood so little that even after 30 minutes of inhaling carbon monoxide this blood barely contains any carboxyhaemoglobin. The methods of determining the amount of blood take into account only the circulating and not the stored blood. Due to a relatively lower plasma content the number of erythrocytes in the stored blood is 20 to 40 per cent higher than in the circulating blood.

The liver and lungs as blood depots. The liver may be regarded as a depot though the blood it contains is not excluded from the general blood flow. Constriction of the hepatic veins leads to a state in which more blood temporarily flows into the liver than out of it. The surplus is stored in the distending vessels of the liver. The structure of this depot is shown in Fig. 55 (bottom).

The same thing may occur in the lungs. Depending on the degree of dilatation the vessels of the lungs, like those of the liver, may hold varying amounts of blood.

The skin as a blood depot. A certain incomplete exclusion of part of the blood from the general circulation is also observed in the so-called by-pass (Fig. 55), even less complete in the middle, during the dilatation of the vascular channel of the skin (see bottom of Fig. 55). By dilating the vessels of the subpapillary layer can also hold a considerable amount of blood (up to one litre). This blood is not mobile and is retained here, while the blood flows rapidly only through the capillaries which form a sort of "*short circuit.*" The arterial-venous anastomoses encountered in certain parts of the skin, by dilating, aid the blood which flows through the skin considerably to by-pass the subpapillary rete of the capillaries and the venules. The dilatation of these plexes, consequently, leads to a temporary exclusion of a considerable amount of blood from circulation in the vascular system. The flow of the blood into the vascular anastomoses of the skin of the lower extremities probably explains why the amount of the circulating blood decreases in many people when they assume a vertical position.

CHAPTER 16

MECHANISMS REGULATING THE VASCULAR TONE

Having considered the conditions determining the flow of blood through the different divisons of the vascular system we must examine the mechanisms which regulate the blood pressure and the blood flow to various organs. This regulation (we shall not consider the changes in the work of the heart for a time) involves primarily the width of the different divisions of the vascular channel, mainly the arterioles which I. Sechenov termed the *taps* of the vascular system.

Vascular Tone

The lumens of all vessels are determined chiefly by the state of their smooth musculature, while those of the capillaries, probably, by the state of the endothelial cells and of the smooth musculature of the precapillary sphincters.

In the large arterial trunks (aorta, innominate artery) the amount of muscular elements is small compared with the elastic tissue; in the arteries of a lesser diameter the thickness of the muscular layer increases in comparison with their total thickness, while in the arterioles the muscular elements form the main mass of the vascular wall. Most of the smooth musculature of the vessels is formed of circular fibres.

Smooth muscles are characterized by their capacity for sustained contraction and tension. Sustained tension of a muscle without signs of fatigue is referred to as the *tone of the muscle*. When the tone of the smooth circular musculature is high the lumen of the vessels is small. Even considerable pressure within the vessel cannot greatly stretch the musculature and does not lead to an appreciable dilatation of the vascular lumen. Contrariwise, when the musculature has a low tone the lumen of the vessels is wide and a rise in the intravascular pressure dilates the vessels still more. Thus, the *size of the arteriolar lumen is determined by the tone of the smooth circular musculature of the arterioles.*

Vasoconstrictor Nerve Fibres

Sympathetic nerve fibres run to all blood vessels and connect the smooth vascular muscles with the central nervous system. They arise from the thoracic and upper lumbar segments of the spinal cord in its anterior roots and reach the cells of the sympathetic ganglia from which postganglionic fibres run to the vessels.

Vasoconstrictor effect of the sympathetic nerve fibres. The impulses transmitted over the sympathetic nerve fibres constrict the vessel, mainly the arterioles, in a number of regions of the circulatory system. In 1842, A. Walther noted a dilatation of the vessels in the foot of the frog after cutting the sympathetic fibres of the sciatic nerve. It was later found that if the sympathetic nerve was cut in the neck the skin of the head and of the ears grew red and warmer. When the peripheral portion of the severed sympathetic nerve, in this case the portion running to the head, was stimulated the skin which turned red after the nerve had been cut grew pale and cold. This experiment is particularly effective if we judge about blood filling by the colour of the white rabbit's ear. It was precisely in such an experiment on the rabbit's ear that Claude Bernard discovered (1851) the effect of cutting and stimulating the sympathetic fibres on the vessels of mammals (Fig. 56). These experiments performed by Walther and Claude Bernard laid the basis for the theory of circulatory regulation.

If we cut the sympathetic fibres running to the head, to the upper or lower extremities or to the abdominal cavity (Fig. 57, left) the denervated vessels will dilate. If we stimulate these nerve fibres the vessels will become constricted (Fig. 57, right). After cutting the splanchnic nerve the vessels of the abdominal cavity dilate and the blood pressure drops. Stimulation of the splanchnic nerve produces a constriction of the vessels of the abdominal cavity which provokes a considerable rise in the blood pressure. The same effect (Fig. 58) is observed when stimulating the spinal cord in the grey matter of which lie the nerve cells whose axons (sympathetic preganglionic fibres) transmit the vasoconstrictor influences (the fibres of the splanchnic and other nerves).

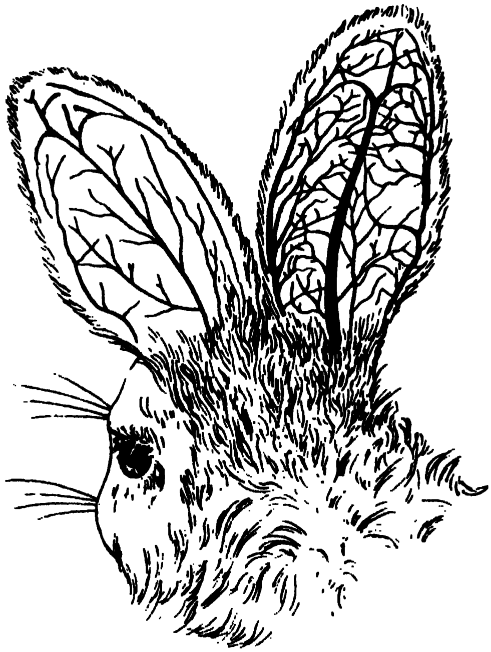


Fig. 56. Blood vessels in the rabbit's ear; on right side where vessels are sharply dilated sympathetic trunk is cut (experiment by Claude Bernard).

It follows from these facts that the sympathetic nerve fibres constrict the vessels of the skin and the vessels of the organs of the abdominal cavity; they are, therefore, called *vasoconstrictor nerves* or *vasoconstrictors*. The *vasoconstrictor sympathetic nerve fibres propagate impulses which increase the tonic contraction of the circular musculature of most of the arterioles* of the abdominal organs and of the skin.

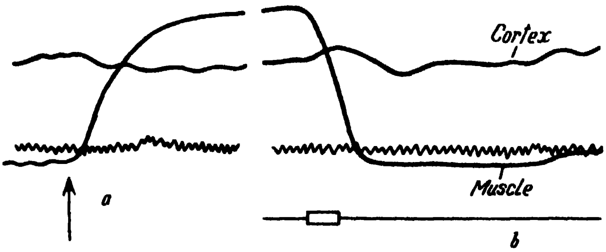


Fig. 57. Effect of cutting *(a)* and stimulating *(b)* the dog's cervical sympathetic nerve on amount of blood flowing through one of the facial muscles (see designation "muscle") and through parietal region of cerebral cortex.

Middle line shows blood pressure. Left—sympathetic cervical trunk has been cut at moment indicated by arrow; right (during the time shown by white rectangle) its distal portion (running cephalad) is stimulated (after B. Klosovsky).

The vessels of the upper extremity are innervated by fibres given off by the cells located in the lower cervical and the upper thoracic sympathetic ganglia; the vessels of the head are innervated by fibres arising from the cells of the cervical ganglia;

the vessels of the abdominal cavity are innervated by fibres mainly of the splanchnic and mesenteric ganglia; the vessels of the lower extremities receive fibres of the *X-XII* thoracic and of *I-III* lumbar ganglia. The sympathetic vasoconstrictor fibres run to the vessels of the abdominal cavity in the trunk of the splanchnic nerve, while to the vessels of the extremities they travel in two ways: together with the vessels by running in their walls and in large nerve trunks running off from the latter to the vessels.

The vasoconstrictor action of the sympathetic nerve fibres is clearly pronounced as regards the vessels of the skin, the abdominal organs, the kidneys, the meninges and, apparently, the lungs. The sympathetic fibres do not sharply affect the vessels of active skeletal muscles. Stimulation of the sympathetic fibres dilates the vessels of the heart.

Constriction of capillaries and veins is observed in response to the stimulation of the sympathetic nerve fibres, but after denervation of the capillaries they show transient dilatation. However, little is known about the innervation of capillaries and veins as yet.

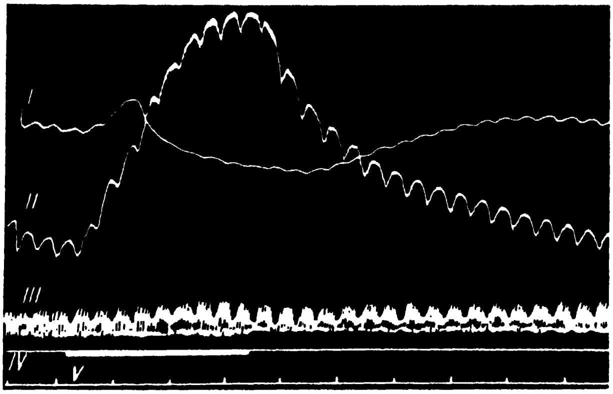


Fig. 58. Rise in blood pressure and constriction of vessels in abdominal cavity in response to stimulation of cervical ion of spinal cord below medulla oblongata by ction current (experiment by Ludwig and Thiry).

d pressure; *III* -
ntervals (15 seconds).

Tone of vasoconstrictor nerves. A severance of the vasoconstrictor sympathetic fibres causes the arterioles they innervate to dilate. It follows that they are constantly in a state of tonic excitation which continuously maintains the circular vascular musculature in a certain degree of tonic tension. The higher the tone of the vasoconstrictor fibres, the more constricted the arterioles they innervate; the lower their tone, the more are the arterioles dilated.

The level of excitation of the vasoconstrictors, which is itself dependent on the state of the corresponding nervous centres (see below), determines the extent to which the arterioles—the "taps" of the vascular system—open.

Vasodilator Nerve Fibres

In addition to vasoconstrictor nerve fibres there are also vasodilator fibres whose excitation causes the vessels to dilate. Claude Bernard discovered their existence by showing that stimulation of the branch of the hypoglossal nerve which runs to the submaxillary gland—the so-called chordae tympani—caused the vessels of this gland greatly to dilate. Several times the usual amount of blood flows out of the veins of the salivary gland during the stimulation of the chordae tympani. The vessels of the gland dilate to such an extent and the resistance they offer to the flow of the blood drops so much that even the pulsations produced by the ventricular systoles are transmitted to the stream of the venous blood. The venous blood which flows from the salivary gland at this time is scarlet-red like the arterial blood.

Following the discovery of the vasodilators in the chordae tympani they were also discovered for the tongue vessels in the hypoglossal nerve (where these fibres enter from the chordae tympani) and in the pudendal nerve. There are vasodilator fibres or *vasodilators* in most of the other nerve trunks, but they are harder to discover there (for example, in the sciatic nerve) because the vasoconstrictor sympathetic fibres also run in the same trunks. During normal stimulation of such mixed nerves the vasoconstrictor effect resulting from the excitation of the vasoconstrictors exceeds the effect produced by the simultaneous excitation of the vasodilators. If the peripheral portion of a mixed nerve is stimulated 4 to 5 days after its severance only a dilatation of the vessels is observed; the vasoconstrictor fibres have already degenerated while the vasodilators are still intact.

Claude Bernard

Dilatation of the vessels not disguised by the effect of the simultaneous excitation of the vasoconstrictors is also noted if the mixed nerve is stimulated by induction-current shocks (A. Ostroumov) following each other infrequently (at intervals of 1 to 3 seconds). At this low frequency of stimulation the vasoconstrictors are not excited and only the vasodilators are stimulated.

The question of the morphological nature of the vasodilator fibres, whose excitation causes the vascular musculature to relax and the vessels to dilate, presents considerable difficulties.

The question of the vasodilator fibres of the chordae tympani and of the fibres of the hypoglossal and the pudendal nerves is decided simply: there it is the fibres of the parasympathetic nervous system that act as vasodilators. But this does not mean that all vasodilator fibres belong to the parasympathetic system and that all parasympathetic fibres dilate the vessels (the parasympathetic fibres running to the vessels of the heart do not dilate but constrict them; p. 179).

No definite parasympathetic fibres running to the vessels of the extremities, the skin and the skeletal muscles have been discovered. It has been found, however, that the vasodilator nerve fibres (except the vasodilators running to the chordae tympani and in the hypoglossal and pudendal nerves) arise from the spinal cord in its dorsal roots which since the time of Magendie have been thought to contain only afferent nerve fibres (Law of Magendie). Bayliss has furnished serious data in favour of the fact that this exception to the Law of Magendie is only apparent. As a matter of fact nerve fibres are able to propagate excitation in both directions and to branch. The axon of an afferent neuron, i.e., an afferent nerve fibre, may divide into two branches of which one runs to the receptor and the other to the wall of a blood vessel. This branching of an afferent fibre was very clearly observed in B. Lavrentyev's preparations. The dilatation of the vessels which occurs when the posterior roots are stimulated may, therefore, be due to propagation of the excitation along the axons of the sensory (afferent) neurons, one branch of which terminates at a receptor and the other ends in the wall of an arteriole, a precapillary or even a capillary. The excitation received by a receptor may run along an afferent fibre to the point of its division and passing to the branch, which runs to a vessel, be propagated from the point of division back to the periphery (*antidromically*, as it is sometimes referred to) to the musculature of the vessels. In such cases the smooth musculature relaxes and its tone is depressed.

Transmission of stimulation from a receptor to an effector due to the propagation of excitation within the limits of the division of an axon of one neuron is called an *axon-reflex*.

The fact that stimulation of a small portion of the skin may cause the dilatation of the cutaneous vessels in portions removed from the point of stimulation even after all the nerve trunks running to these portions are cut is an important argument in favour of this point of view. However, the effect disappears several days after severance of the nerves when the latter degenerate.

Some investigators deny the existence of axon-reflexes. It is scarcely right to do so since it is hard to assume that the incontestably established (Lavrentyev) division of afferent fibres which terminate at effectors should be of no functional significance. At the same time there is no doubt that a number of phenomena formerly designated as axon-reflexes are really due to a transfer of excitation from afferent to efferent neurons on the periphery (p. 534).

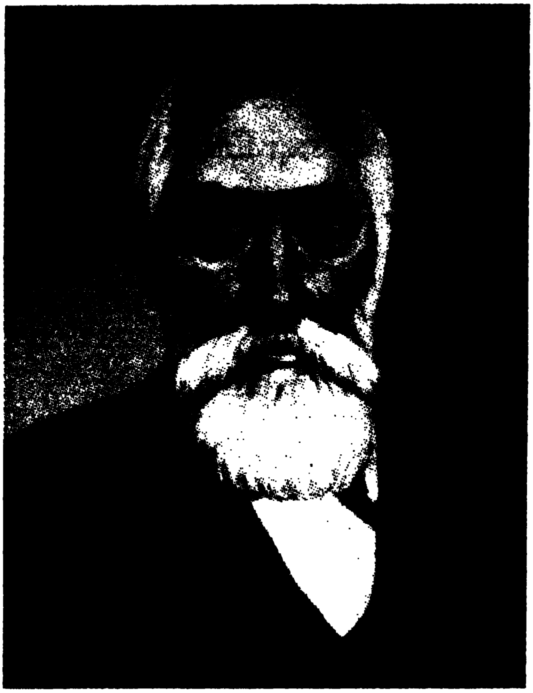
Significance of the peripheral nerve structures in the vascular walls of the tissues for reactions of the vascular musculature. The tone of the vessels does not fully disappear when some vascular region is separated from the central nervous system (by severance of all the nerve fibres which run to it). A rapid rise in pressure in the arterial system and an injection of stimulating substances into the arteries (for example, a concentrated NaCl solution) cause a constriction of the vessels and lead to a rise in the blood pressure. When stimuli are applied to the arterial system a constriction of the vessels is observed even after the degeneration of all the nerves at the corresponding vascular region. Acetylcholine and novocain remove these vascular reactions without decreasing the constriction of the vessels stimulated by adrenalin. It is probable that the peripheral nervous structures, which normally always function under central influences, are able after the exclusion of the latter to ensure a certain peripheral regulation of the vascular tone.

Vasodilator effect of the sympathetic nerve fibres. Excitation of the sympathetic fibres may lead to a dilatation of the vessels of the skeletal muscles; it also dilates the vessels of the heart. Some data testify to the fact that under certain conditions the vessels of the abdominal organs may also dilate under the influence of excitation of *sympathetic* nerve fibres. This is confirmed by the dilatation of the vessels of internal organs when the splanchnic nerve is stimulated after the introduction of certain poisons (ergotamine, etc.) and by the dilatation of the abdominal vessels sometimes observed in response to the stimulation of the sympathetic chain in high blood pressure. However, the assumption that there are special vasodilator sympathetic fibres, which always exert only a vasodilator influence, is hardly correct. It is more probable that depending on the frequency and nature of the impulses of excitation and on the condition of the vascular musculature the same fibres may produce different effects—contraction and relaxation of the smooth musculature of the vessels. This is confirmed by the experiments in which the splanchnic nerve is stimulated after application of ergotamine and by the drop in the blood pressure during continued administration of very large doses of adrenalin, which is a sympathetic "mediator."

The idea that the same nerve fibres may act differently in no way contradicts the fact that *under usual conditions* the excitation of the sympathetic fibres running to the vessels of the skin and of the abdominal organs leads to their constriction, whereas excitation of the posterior root fibres (apparently afferent) dilates the vessels of the skin and of the skeletal muscles. Under special conditions certain sympathetic fibres cause a dilatation of the vessels of the internal organs as they usually dilate the vessels of the heart.

Vasomotor Centre

The nerve fibres, which run to the blood vessels and cause their constriction or dilatation, are but conductors of excitation which under normal conditions arises only in the central nervous system, in its so-called vasomotor centre. The vasomotor centre implies the aggregate of the structures of the central nervous system which affect the blood vessels. It includes the structures of the central nervous system from the spinal cord to the cerebral cortex which by their activity condition the state of the vascular system.


F. Ovsyannikov

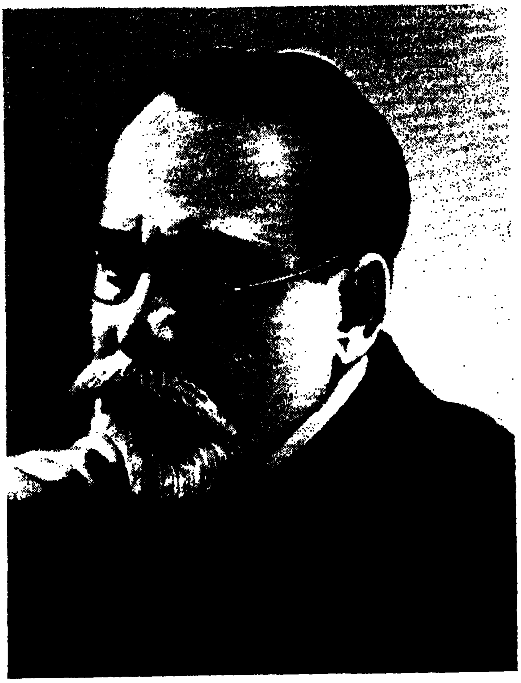
Spinal vasoconstrictor neurons. The nerve cells whose axons form the vasoconstrictor fibres arising from the spinal cord are located in the lateral horns of the thoracic and the three upper lumbar segments of the spinal cord. These cells have been given the name of "spinal vasoconstrictor centres" though this term is acceptable only for purposes of abbreviation because these spinal structures normally never function apart from the higher divisions of the central nervous system.

After severance of the spinal cord in dogs in the region of the lower cervical segments it is barely possible for 3 to 4 weeks to produce the vasoconstrictor reflexes described below. Consequently, the spinal centres of the vasoconstrictor fibres are normally under the constant influence of higher divisions of the central nervous system and must be regarded as the terminal link in the system of the central structures which form a single vasomotor centre.

Bulbar division of the vasomotor centre. The spinal vasoconstrictor neurons continuously receive impulses from a definite region in the medulla oblongata, from a group of cells in the floor of the IV ventricle. This was demonstrated by the experiments performed by F. Ovsyannikov in K. Ludwig's laboratory in 1873. The experiments showed that cutting the spinal cord below the medulla is usually accompanied by a certain drop in the blood pressure (to 60 to 80 mm. Hg, and frequently even lower). After the spinal cord is separated from the medulla the tone of the vasoconstrictors somewhat decreases. Cutting the brain stem above the medulla oblongata does not produce these changes and does not lead to a disappearance of the vascular reflexes which always occurs after a separation of the spinal cord from the medulla. Stimulation of very definite portions of the medulla oblongata or of the conduction paths, which run from the medulla to the spinal cord, causes a sharp rise in the blood pressure due to a constriction of the vessels (Fig. 58). It is, therefore, believed that excitation in the spinal vasoconstrictor centres normally always arises under the influence of excitation of the so-called chief vasomotor centre in the medulla oblongata.

No investigator has as yet been able to keep homoiotherms with the cerebrum extirpated above the medulla oblongata alive for any length of time. Such animals live only a few hours (24 hours at most) and die of circulatory and respiratory disorders. We must, therefore, necessarily recognize that the bulbar division of the vasomotor centre (this designation is more appropriate than the deep-rooted term "chief vasomotor centre") is under the constant influence of higher divisions of the central nervous system.

Stimulation of the portions of the medulla oblongata located in the immediate proximity of the vasoconstrictor centre leads to a dilatation of the vessels accompanied by a drop in blood pressure. This warrants the assertion that the vasodilator nerves have a certain tone.



V. Danilevsky

Very little is known of the role of the midbrain and the cerebellum in regulating the vascular tone. Considerable variations in blood pressure (always connected with changes in respiration) are frequently noted after cutting the cerebral division on the level of the red nuclei (decerebration, see p. 230). It has been impossible, however, thus far to discover the laws which govern these variations. Variations in blood pressure were noted in L. Orbeli's laboratory during stimulation of the cerebellum; it is still difficult to explain their mechanism; they may be connected with the influences which the cerebellum exerts on the sympathetic system due to its relation to the cerebral cortex.

The diencephalon, especially the different nuclei of the hypothalamus, is usually regarded as the focus of the higher subcortical centres of the entire vegetative nervous system. Stimulation of this division of the central nervous system leads to considerable variations in blood pressure. Dogs and cats, in which the entire cortex has been removed but the diencephalon retained, can live long (if well taken care of) and display rather complexly coordinated cardiovascular (and respiratory) reflexes in the form of rises in the blood pressure and accelerated heart rate during fits of "rage" which they sometimes have without any apparent reason. It is probable that in the newborn with their relatively poorly developed cerebral cortex the structures of the diencephalon play the main part in regulating the circulation. But as the higher division of the central nervous system develops, the influences of the cerebral cortex acquire a special significance in circulatory regulation.

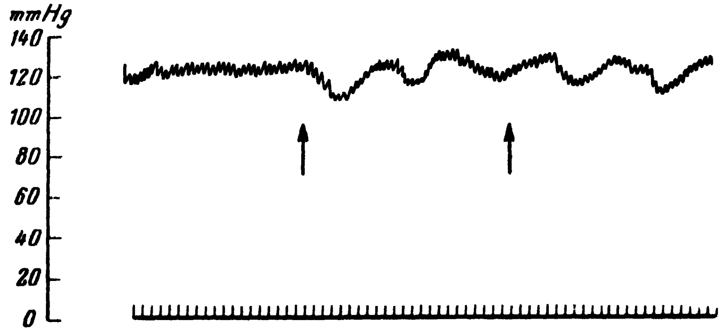


Fig. 59. Effect of stimulating left premotor zone in man by induction current (during cerebral operation) on arterial pressure.

Arrows indicate beginning and end of stimulation (after Koreisha).

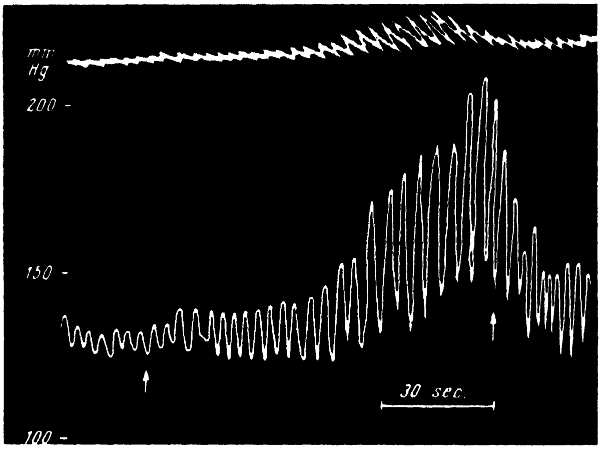


Fig. 60. Effect of asphyxia on the dog's arterial bl pressure.

Top--record made by spring manometer; bottom--record made by mercury manometer; first arrow (left) indicates beginning of asphyxia, second arrow its end.

Stimulation of the cerebral cortex, as was long ago discovered by V. Danilevsky, N. Mislavsky and V. Bekhterev, leads to changes in blood pressure.

Effect of chemical substances on the vasomotor centre. Chemical agents circulating in the blood may affect the innervation of the vessels (and the heart) by stimulating the chemoreceptors and by directly stimulating the vasomotor centre. This is revealed in the action of carbon dioxide on the vasoconstrictor centre (Fig. 60) discovered as early as the sixties of last century by N. Kovalevsky and M. Traube. Inhalation of carbon dioxide (and asphyxia) considerably raises the blood pressure because of the resulting constriction of the blood vessels. This result is also retained after denervation of the aortic and sino-carotid zone (see below) and is observed in a weakened form (in an acute experiment) even after removal of the cerebrum including the medulla oblongata. In the latter case the rise in blood pressure during accumulation of carbon dioxide in the body is due to its influence on the vasoconstrictor neurons of the spinal cord (as before stated, these neurons hardly react to the impulses from the afferent nerve fibres for a long time after being disconnected from the higher centres).

Carbon dioxide is, possibly, the only chemical compound always present in the body which, brought to the structures of the central nervous system by the blood, directly excites the vasoconstrictor centre and the centre of the vagal fibres which inhibit the heart. The nervous elements of these central structures are similarly affected by a rise in intracranial pressure. Preparations of foxglove are pharmacological agents which stimulate the inhibiting innervation of the heart and the vasoconstrictor centre.

Oxygen deficiency in the blood stimulates the vasoconstrictor and vagal centres only reflexly by stimulating the receptors of the aortic and the carotid zones (p. 161) and, probably, the chemoreceptors of different tissues. In animals with a denervated aortic and sino-carotid zones inspiration of air poor in oxygen leads to a gradually developing paralysis of the vasoconstrictor centre without its excitation phase.

Effect of Hormones and Various Metabolites on the Vessels

The nervous influences on the blood vessels are permanently connected with those exerted by certain hormones, i.e., specific chemical agents produced only in definite organs.

Effect of adrenalin on the vessels. Adrenalin markedly constricts the arterioles and arteries of the skin, the organs of the digestive tract, the kidneys and the lungs, but dilates the vessels of the heart.

The vessels of a resting skeletal muscle are apparently somewhat constricted under the influence of adrenalin only when it is present in the blood in low concentrations; in high concentrations adrenalin frequently causes the vessels of the muscles to dilate. During muscular work, when the secretion of adrenalin is increased, the vessels of the skeletal musculature are not constricted under its influence, whereas the constriction of the vessels of the abdominal organs, which occurs under the effect of adrenalin, ensures a greater flow of blood to the muscles.

Fig. 61 shows the effect of different doses of adrenalin on the arterial blood pressure. A very small amount of adrenalin is enough to cause a considerable rise in blood pressure due mainly to the constriction of the lumen of the small arteries of the abdominal cavity and of the cutaneous vessels. The dose of adrenalin sufficient to cause a constriction of the vessels is approximately 0.0002 mg. per kg. of body weight (if injected directly into the blood). Injection of 0.5 to 1 mg. of adrenalin into the blood of man causes a tremendous (up to 200 to 300 mm. Hg) but very transient rise in blood pressure.

Adrenalin also constricts the capillaries, probably by acting on the precapillary sphincters. The veins, apparently, also become constricted as adrenalin enters the blood.

During muscular rest the medulla of the adrenals secretes but very little adrenalin. The activity of the medulla of the adrenals, therefore, hardly plays any part in maintaining the tone of the arterioles at rest. During hard muscular work and under so-called emotional stress the increased secretion of adrenalin aids in increasing the blood flow through the skeletal muscles, the brain and the heart because it produces a rise in the blood pressure hardly constricting (and perhaps even dilating) the vessels of these organs.

The medulla of the adrenals is innervated by fibres of the splanchnic nerve. Stimulation of this nerve causes the adrenals to secrete adrenalin (Cheboksarov, 1910).

The hormone of the posterior lobe of the hypophysis (vasopressin) produces a strong constricting effect on the arterioles and the capillaries. This has been demonstrated by experiments on animals; the animals were injected a preparation of the hypophysis and the effect of this injection was studied on isolated arteries. However, removal of the hypophysis hardly affects the vessels (incidentally, vasopressin may, possibly, also be produced by the cells of the hypothalamus).

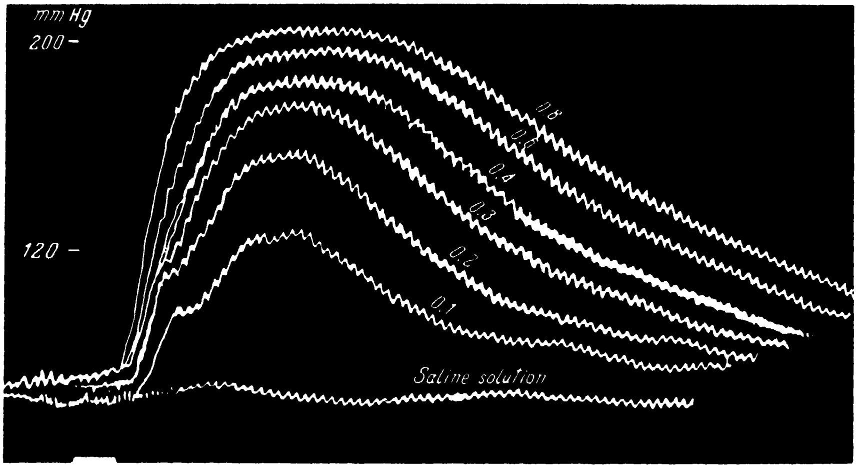


Fig. 61. Effect of intravenous injection of different amounts of adrenalin (0.1-0.8 mg.) on the dog's arterial blood pressure.

Figures above curves indicate amount of adrenalin injected: bottom—effect of intravenous injection of saline solution on blood pressure (after Elliott).

The hormone of the adrenal cortex is, apparently, very important in maintaining the normal state and permeability of the capillaries. Twenty to forty hours after removal of the adrenals the capillaries dilate and retain a lot of blood while the pressure in the arteries drops. Injection of the hormone produced by the adrenal cortex into the blood of animals with removed adrenals restores their normal circulation.

Effect on the vessels of substances produced by the kidneys. It was found as early as 1898 that an injection of an extract of renal tissue into the blood caused a constriction of the blood vessels (arterioles) and a rise in the arterial blood pressure. Tiegerstedt, who discovered this fact, proposed that the substance produced with the aid of the kidneys and causing constriction of the arterioles be named *renin*. This fact had attracted no attention;* later it was found that a partial compression of the renal arteries which limited the blood flow through the kidneys, i.e., produced renal ischaemia, resulted in a stable rise in arterial blood pressure (hypertension). The rise in blood pressure is caused by a stable constriction of the arterioles, mainly those of the abdominal organs.

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* In the beginning of 1899 I. Pavlov also pointed out the possibility of producing substances, which influence the circulation, by a "damaged" kidney.

Constriction of the vessels responsible for a sustained rise in the blood pressure with partial clamping of the renal arteries, is not due to a limitation of the secretory function of the kidneys. In renal ischaemia the pressure may rise even when their secretory function is entirely unaffected, while, on the other hand, impairment of the secretory activity of the kidneys does not lead to a rise in the blood pressure for a long time.

Compression of the renal vessels, which causes a certain degree of ischaemia (insufficient blood supply) of the kidneys for a long time, is effected by special clamps placed on the renal arteries; the clamps are fastened so as to reduce the lumen of the renal artery to at least half its size (Goldblatt). Renal ischaemia may cause hypertension both after denervation of the kidneys and of large vascular regions, but it does not in any way warrant the conclusion that the central nervous system does not influence the production of renin and its activity under normal conditions when the innervation of the kidneys and the vessels is intact.

The extracts containing the purest renin do not constrict the vessels of the isolated organs through which they are perfused in a physiological solution. Suffice it, however, to add a little blood *plasma* to the solutions containing renin to produce the typical vasoconstrictor effect. It follows that the plasma contains a substance in the presence of which renin is activated. This substance was named ***renin-activator***. Under the action of the renin-activator renin forms a new compound—***hypertensin***. Hypertensin is just the agent which produces the marked vasoconstrictor effect. It is extraordinarily active, approximating the activity of adrenalin which causes constriction of the vessels in a 1 : 10,000,000 dilution (and sometimes even in lower concentrations).

Renin, renin-activator and, consequently, hypertensin, which results from their interaction, are protein bodies or products of their hydrolysis. Renin-activator is a polypeptide with a molecular weight of about 2,700.

There are reasons to believe that the production or the increase in production of renin is a normal physiological reaction which occurs reflexly in response to the action of factors leading to a drop in the blood pressure. This is confirmed by the fact that after blood losses the blood contains more hypertensin than normally, probably because of an increased passage of renin from the kidneys into the blood. Production of renin may, thus, aid in restoring normal blood pressure when the latter is somewhat lowered.

It is not clear yet why a reduced blood flow through the kidneys increases the passage of renin into the blood and by virtue of this increases the production of hypertensin. Normal kidneys contain a special enzyme—hypertensinase—which destroys renin. It is assumed that this enzyme disappears or becomes inactive when insufficient blood flows through the kidneys. Owing to this ischaemia of the kidneys leads to an increase in the concentration of hypertensin in the blood. This matter has not yet been finally settled, however.

Vasoconstrictor effects connected with renal activity. An interesting phenomenon pertaining to the regulation of blood pressure was discovered in dogs who were kept alive for 20 days after removal of both kidneys. These dogs developed typical hypertension. This was not due to the pressure of the substances, which are normally eliminated with the urine, because the dogs whose ureter ends were sewn into the vena cava retained a normal blood pressure almost to the very death.

There are indications that the kidneys contain special aminoxydases which oxidize the amino-group of compounds that produce a vasoconstrictor effect.

Effect of the products of tissue metabolism on vascular tone. In addition to, and in connection with, the nervous influences reaching the vessels from the central nervous system and the influences of the hormones produced by the endocrine glands the vessels are also affected by the products of metabolism formed in all the tissues and organs. The compounds resulting from tissue metabolism dilate the blood vessels of the organs in which they are formed. Of these compounds the following are of special importance:

1. *All compounds of an acid nature*, particularly carbonic acid, the formation of which leads to an increase in the concentration of H-ions in the tissues.
2. *Histamine*, an amine formed from histidine under the action of a special enzyme and causing dilatation of the capillaries already in a concentration of 0.001 mg. per kg. of body weight. Histamine is, apparently, liberated during the excitation of a number of afferent nerve fibres. It is formed under the action of agents which injure the skin. The reddening of the skin due to burns, mechanical irritation or inflammation partly results from dilatation of the capillaries produced by the influence of histamine.
3. *Acetylcholine*, a chemical compound formed at the endings of the vasodilator nerves. Acetylcholine causes extensive dilatation of the arterioles and a drop in the blood pressure.
4. A number of products of metabolism compounds of phosphorus in the tissues, especially, *adenylic acid.*

For the significance of the production of these substances and the mechanism of their action see p. 175.

CHAPTER 17

REFLEX REGULATION OF CIRCULATION

Reflex Influences on Circulation from the Receptors of the Large Vessels

Cyon and Ludwig found (in 1866) that a nervous branch containing *afferent* fibres ran alongside the vagus in the rabbit (in other animals in their trunks). These fibres connect the receptors located in the wall of the aortic arch, in the aortic bodies and under the endocardium of the left ventricle with the medulla oblongata. Their stimulation reflexly causes a drop in the arterial blood pressure (Fig. 62). The fall in the arterial blood pressure during the stimulation of the afferent fibres running from the aorta is conditioned, firstly, by a slowing down of the heart rate which results from reflex excitation of the centre of the vagus in response to the stimulation of the aforesaid receptors; secondly, it is due to a dilatation of the vessels (especially those of the abdominal cavity), which occurs as a result of a reflex inhibition of the vasoconstrictor centre.

Cyon and Ludwig named the nerve they discovered a *depressor* emphasizing by this that excitation of this afferent nerve leads to a reflex *drop* in the blood pressure. The afferent fibres running from the receptors of the aortic arch are often also called the aortic nerve; some authors believe that it also has fibres whose stimulation may reflexly raise the blood pressure.

A *rise* in the blood pressure in the aorta which causes a distention of its walls is a natural stimulus of the receptors of the aortic nerve. This distention of the aortic walls acts as a mechanical stimulus on the receptors located in the aortic walls and representing a typical example of interoceptors. They are vascular *presso-* or *baroreceptors* and, consequently, belong to the group of mechanoreceptors.

Analogous receptors were discovered about 60 years after Ludwig and Cyon at the site where the common carotid artery divides into the external and internal carotid arteries (Fig. 63). Here in the carotid sinus (*sinus caroticus*) there is a complex nervous structure which in addition to sensory nerve endings contains a number of nerve cells. The afferent fibres running from the carotid sinus are called the *carotid* or *sinus nerve* (it is sometimes designated as Hering's nerve); the fibres enter the trunk of the glossopharyngeal nerve (the IX pair of the cranial nerves) and run to the medulla oblongata.

The significance of the baroreceptors of the carotid sinus is generally analogous to that of the baroreceptors of the aortic arch. That is why reference is frequently made to the receptors of the aortic-carotid or the aortic-sino-carotid zone. The receptors of the carotid sinus, like those of the aorta, are excited by a rise in the blood pressure. Excitation of their afferent fibres reflexly lowers the tone of the vasoconstrictor centre and raises the tone of the centre of the cardiac fibres of the vagus; this results in a dilatation of the vessels (mainly the arterioles) and in a slowing down of the heart rate. According to some data the baroreceptors of the carotid sinus are normally capable of greater excitation than those of the aorta.

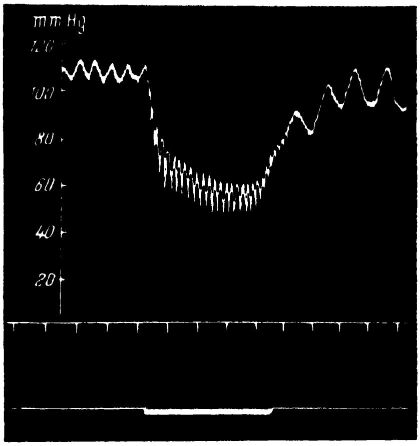

Fig. 62. Effect of stimulating central portion of severed aortic nerve (depressor) by induction current on the rabbit's blood pressure.

From top to bottom: record of arterial pressure, time intervals (5 seconds) and stimulation mark.

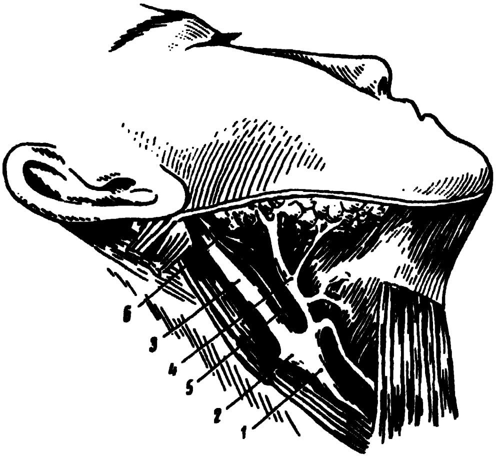

Fig. 63. Topography of carotid sinus in man (after Heymans).

1— common carotid artery; *2*— carotid sinus; *3* and *4*— external and internal carotid arteries; *5*— carotid nerve; *6*— glossopharyngeal nerve.

In an experiment, as it was first done by Y. Moiseyev, it is possible to insert a glass tube (a canula) into the common carotid artery and into one of its branches, tying off all the other branches. By connecting the canula in the common carotid artery with a pressure reservoir in which the pressure of the liquid can be fixed on any level corresponding to the aims of the experiment, it is possible to create a different pressure in the region of the carotid sinus, which is excluded from the general circulation but retains the nervous connection of its receptors with the central nervous system. It is easy to determine by this method the effect produced on the general arterial pressure of the variations in pressure in the carotid sinus and the effect of various chemical substances added to the liquid perfused through the vessels of the sinus on the receptors of the latter. In a more complicated form of the experiment the region of one or both of the carotid sinuses of the given animal is connected with the circulation of another animal. For this purpose the vessels of the sinus (with the nerves intact) of one animal are connected by canuli and tubes with the vessels of another animal and special precautions are taken against coagulation of the blood (Heymans).

Normally when the carotid sinus is included in the circulation the blood pressure in the carotid arteries during systole is 100 to 120 mm. Hg. If this pressure is created in the perfused sinus a nearly similar blood pressure is established, but if the pressure in the perfused sinus is raised to 180 to 200 mm. Hg the arterial blood pressure drops below normal. Contrariwise, if the pressure of the liquid passed through the carotid sinus is low the blood pressure in the arteries turns out abnormally high (180 to 220 mm. Hg).

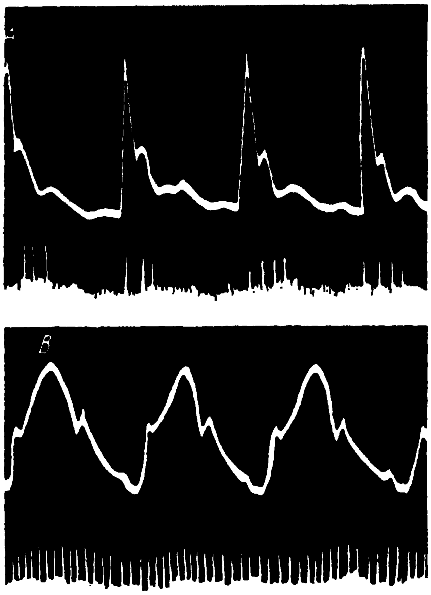

Fig. 64. Action currents (vertical lines in lower part of *A* and *B*) in individual fibre of carotid nerve depending on blood pressure (upper curves).

In experiment *A* arterial pressure was 55 mm., in experiment *B* 135 mm. (after Bronk).

We must necessarily conclude from these experiments that already in normal variations in the arterial blood pressure during the cardiac cycle (60 to 120 mm. Hg) the receptors of the aortic arch and of the carotid sinus become excited and send to the central nervous system impulses which moderate the tone of the centre of the vasoconstrictor nerve fibres and excite the tone of the centre of the vagal fibres which inhibit the heart.

The studies of bio-electric potentials (action currents) of the fibres of the aortic or carotid nerve led to the discovery that the lower the pressure in the carotid sinus, the less frequent the impulses of excitation arising in its receptors. The effect of an acceleration of the impulses, which run from the baroreceptors of the aortic arch and of the carotid artery to the centres, is an increasing inhibition of the vasoconstrictor centre and a growing stimulation of the centre of the vagal fibres which inhibit the heart.

Consequently, the higher the pressure in the aortic arch and in the carotid sinus, the stronger the nervous influences which reflexly lead to a drop in the blood pressure.

The impulses in the carotid nerve are sharply accelerated during each systole and do not completely disappear during diastole; this means that already during the usual diastolic pressure there is a slight stimulation of the baroreceptors in the aortic-carotid zone, which reflexly somewhat inhibit the excitation of the vasoconstrictor centre, and cause a certain excitation of the centre of the vagal fibres that inhibit the heart; during each systole the walls of the arteries distend, stimulation of the receptors of the aortic-carotid zone increases and the reflex influences exerted by their impulses at this time grow.

If the impulses from the baroreceptors of the aortic-carotid zone do not reach the central nervous system, the vasoconstrictor centre is highly excited, the arteries are very much constricted, the vagal tone drops, the heart rate is fast and the blood pressure is abnormally high. Thus, for example after severance of the aortic and carotid nerves the blood pressure of the dog rises to 180 to 220 mm. Hg and does not return to normal for a long time (according to some data it never returns to normal).

Compression of the common carotid arteries, i.e., exclusion of the carotid sinuses from the circulation, similarly removes the stimulation of their receptors and thus produces the characteristic rise in the blood pressure as long as the carotid arteries are compressed. Contrariwise, in response to the rise in pressure in the region of the carotid sinus (Fig. 65), just as during artificial stimulation of the carotid nerve (Fig. 66), arterial pressure drops. In the first case the vessels of the extremities and of the abdominal cavity are reflexly constricted, in the second case they are dilated.

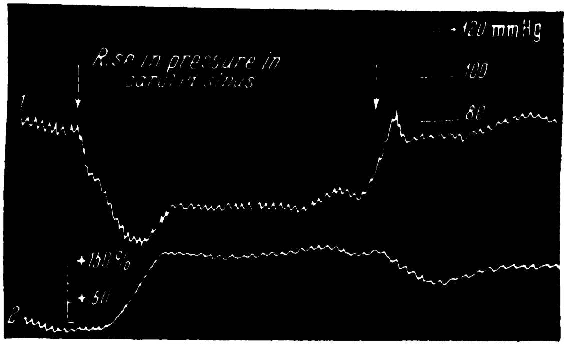

Fig. 65. Effect of blood pressure rise in carotid sinus on arterial pressure *(1)* and on amount of blood *(2)* flowing through femoral artery (after Rein).

During reflex drop in blood pressure resulting from rise in pressure in carotid sinus vessels of extremity dilate.

Under normal conditions the carotid sinus is, of course, never excluded from the circulation and its receptors are affected by the pressure existing in the carotid artery at the given time; it nearly equals the pressure in the

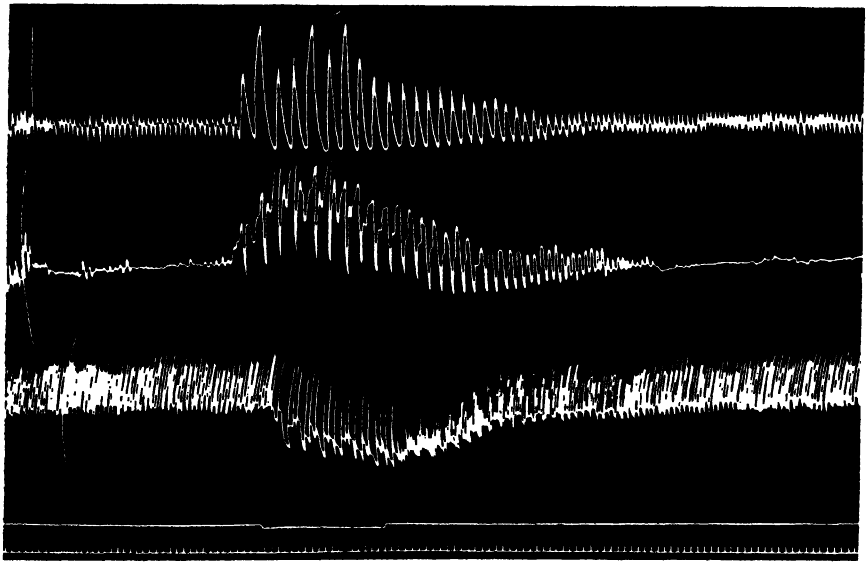

Fig. 66. Record of volume of portal vein (middle curve), arterial pressure (lower curve) and respiration (top) in the dog during fall in arterial pressure produced by stimulation of right carotid nerve (by courtesy of N. Danilov).

aorta which influences the aortic receptors. The higher the arterial pressure the stronger the stimulation of the aortic and carotid receptors. Therefore, if the arterial pressure drops below normal the inhibiting influence reflexly exerted from the receptors of the aortic-carotid zone on the vasoconstrictor centre decreases, the exciting influence exerted by these impulses on the nucleus of the cardiac fibres of the vagus also decreases. The result is an increase in the tone of the vessels and an acceleration of the heart rate, leading to a rise in the arterial pressure. Contrariwise, when the arterial pressure rises above normal the impulses from the receptors of the aortic-carotid zone increases, due to which the vasoconstrictor centre is inhibited and the vagus is excited more than during normal arterial pressure. Inhibition of the vasoconstrictor centre leads to a decrease in the tone of the vessels, excitation of the vagal centre leads to a slowing down of the heart rate owing to which the arterial pressure returns to normal.

The reflexes, which arise during pressure changes in the region of the carotid sinus and the aortic arch, may be characterized as reflexes which equalize the blood pressure; they lead to a rise in the arterial pressure if it is low and to its fall if it is high.

The reflex increase in the tone of the vasoconstrictor nerves usually develops parallel with a decrease in the excitation of the vasodilator nerves (L. Fofanov and M. Chalusov, Bayliss). As the tone of the vasoconstrictors decreases that of the vasodilators simultaneously increases.

With a considerable strengthening or acceleration of the stimulation of the depressor (aortic) or sino-carotid nerve the depressor effect disappears; it reappears as the stimulation is weakened or slowed down (V. Delov).

Thus, strong and rapid stimulation of the baroreceptors of the aortic and carotid zones may inhibit the reaction of the vasomotor centre to the impulses from these receptors; in this case there will be no compensating reflex drop in the blood pressure; the high blood pressure will not fall.

The aortic-carotid zone does not contain only baroreceptors. The carotid body has a mass of chemoreceptors, which are stimulated by changes in the composition of the blood that bathes them. Carbon dioxide and hydrogen ions are their most important stimuli. The chemoreceptors are also stimulated by a drop in the tension of the oxygen dissolved in the blood (p. 157).

The receptor response to the stimulation of the chemoreceptors of the aortic-carotid zone is contrary to the effect produced by stimulation of the baroreceptors of this zone.

An increase in the amount of carbonic acid or a decrease in the amount of oxygen in the blood stimulate the chemoreceptors and reflexly lead to a rise in the tone of the vasoconstrictors and to an increase in the activity of the heart. This explains the rise in blood pressure during inspiration of carbon dioxide in *asphyxia* (cessation of respiration) and in the initial stages of *hypoxia* (oxygen deficiency, p. 183).

Receptors of the Pulmonary Circulation and of the Arteries of the Abdominal Cavity

Receptors have been found not only in the aortic zone, but also in the wall of the pulmonary artery and its branches, in the large arteries of the abdominal cavity and in the venae cavae. The receptors of the pulmonary artery (like those of the aortic-carotid zone) are excited by a rise in arterial pressure, in this case by a rise in pressure in the pulmonary artery. The vessels of the systemic circulation dilate reflexly in response to the excitation of the vessels of the pulmonary circuit; this leads to a drop in the blood pressure and, consequently, to elimination of pulmonary congestion.

During a rise in arterial blood pressure the receptors of the large arteries of the abdominal cavity are also excited, which reflexly leads to equalization of the arterial pressure.

Significance of the Reflexes from the Baroreceptors of the Large Vessels

The reflex regulation of circulation from the baroreceptors of the aortic arch and of the carotid sinus (partly also of the large arteries of the abdominal cavity and of the pulmonary vessels) is responsible for the maintenance of constant arterial pressure.

The maintenance of constancy in arterial pressure in a healthy unanaesthesized animal under widely differing conditions was noted by I. Pavlov as early as 1879-83.

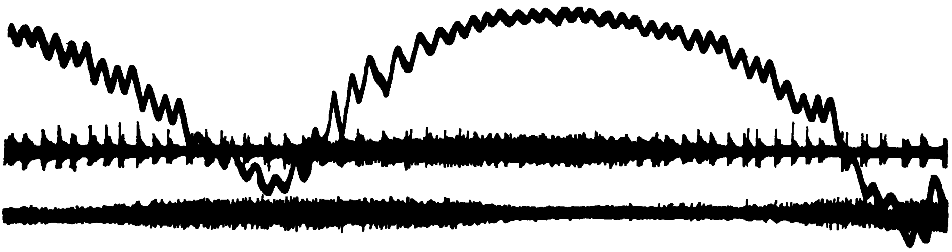

Fig. 67. Changes in bio-currents recorded by oscillograph in cervical sympathetic trunk (lower curve) and in aortic nerve (middle curve) during variations in arterial pressure (waves of third order, upper curve) caused by increase in intracranial pressure in the rabbit.

During each wave showing rise in arterial pressure (somewhat flattened in curve) frequency of bio-currents in aortic nerve, transmitting impulses from baroreceptors of aorta, rises and this results in reflex drop in frequency of impulses in vasoconstrictor sympathetic fibres. Arterial pressure drops, then rises again because of unceasing stimulation of vasoconstrictor centre by high intracranial pressure (after G. Smirnov and K. Bykov).

Pavlov showed that while the vessels of the abdominal cavity dilated the cutaneous vessels were reflexly constricted. In studying the influence exerted on the blood pressure by carbon dioxide accumulating in the body, by bleeding and blood transfusion, Pavlov ascertained that after a disconnection of the vagi these influences caused much greater changes in the arterial pressure than normally because the vagus carried impulses, which reflexly equalized the blood pressure.

There are times in the life of every organism when the absence of compensatory mechanisms would lead to a drop in the arterial pressure (for example, dilatation of the abdominal vessels after eating, increased blood flow to the feet in a vertical position, dilatation of the vessels of the muscles during muscular work and of the vessels of the skin under the action of heat, etc.). At the same time stimulation of a considerable number of exteroceptors usually reflexly leads to a rise in the blood pressure. Whenever the blood pressure rises or drops the impulses resulting from the variations in the stimulation of the receptors of the carotid and aortic zones (as well as other baroreceptors) are responsible for the reflex changes in the activity of the heart and in the state of the vessels and, thus, create the conditions for restoration of the normal level of pressure. Electrophysiological studies make it possible to record a decrease in the number of impulses in the sympathetic nerve during a rise in blood pressure, which causes an acceleration of the impulses of excitation in the afferent fibres of the aortic nerve; this vividly manifests the reflex inhibition of the vasoconstrictor centre (Fig. 67).

If the normal reaction of the receptors of the aortic-carotid zone and, especially, the functional state of the central nervous system are impaired, the regulation of circulation is deranged and the blood pressure easily deviates from the normal.

Reflex levelling-out of blood pressure is an example of reflex regulation in which definite changes in physiological functions are liquidated by reflexes caused by the stimulation of receptors which are themselves stimulated precisely by these changes. These phenomena are often designated as "*auto-regulation.*" This emphasizes the fact that the very fulfilment of a physiological act leads to the rise of reflexes as a result of which the changes causing the given reflex are eliminated.

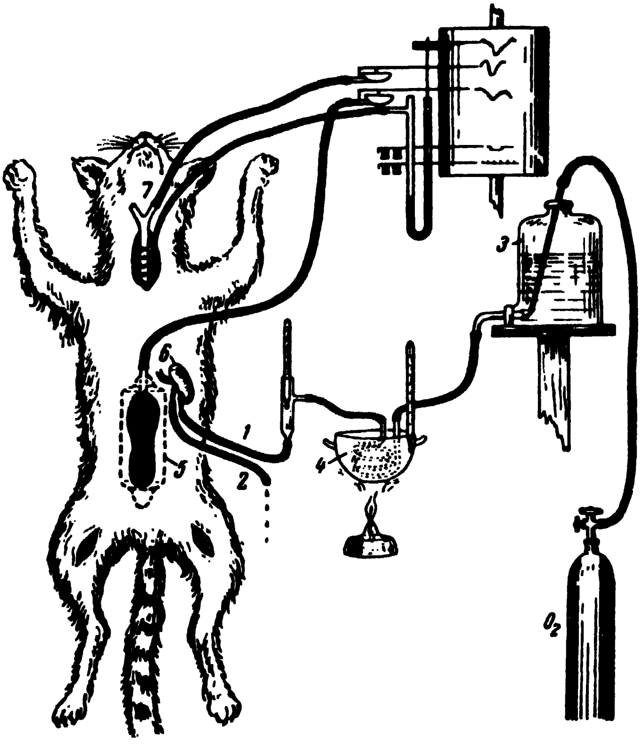

Fig. 68. Diagram of experiments for study of reflex influences arising during stimulation of interoceptors of internal organs via the blood stream.

Canula with afferent tube *(1)* is inserted into artery of spleen *(6)* while efferent tube *(2)* is inserted into vein. Perfused organ is fed fluid from pressure container *(3)*; perfused solution is oxygenated from and heated to body temperature in passing through coil *(4)* immersed in warm (40° C) water. Nervous connections of perfused organ are intact. Kymogram records arterial pressure, volume of intestine (by means of plethysmograph 5) and respiration (through tube 7) (after V. Chernigovsky).

Reflex Influences on the Circulation from the Receptors of the Small Vessels and the Tissues

While many authors believed there were receptors only in the large arteries (aorta, carotid, mesenteric, pulmonary) V. Chernigovsky and his associates (in the laboratory headed by K. Bykov), and later other investigators, showed there were baroreceptors and chemoreceptors in the vessels and tissues of all or nearly all tissues and organs.

The rise in the pressure of the fluid passed through the vessels of the perfused internal organs which retain normal nervous connections reflexly causes a change in the total arterial pressure (as a typical response in some cases—a rise in the total blood pressure). As the pressure in the vessels of the perfused spleen rises the arterial pressure usually also rises reflexly, but as the pressure in the vessels of the intestines, liver and kidneys rises the typical reflex response is a drop in the arterial pressure.

The receptors located in the small vessels or tissues of different organs are also stimulated by various chemical stimuli. Thus, an addition of carbonic acid, lactic acid or acetylcholine to the fluid perfused through the vessels of the organs, which have retained nervous connection with the entire body, causes a rise in blood pressure (Fig. 69) due to the reflex constriction of the arterioles in other vascular regions. Consequently, stimulation of the interoceptors of the internal organs (both baroreceptors and chemoreceptors) reflexly causes mainly a constriction of the arterial vessels (chiefly the vessels of the abdominal cavity). After removal of the cerebrum above the medulla oblongata these reactions are less pronounced.

Baroreceptors and chemoreceptors whose stimulation leads to reflex changes in the blood pressure have been found in the vessels (arterioles and capillaries) and in the tissues of all internal organs of the abdominal cavity, in the sex organs, in the bone marrow (Fig. 70), in the pericardium and, apparently, in all tissues.

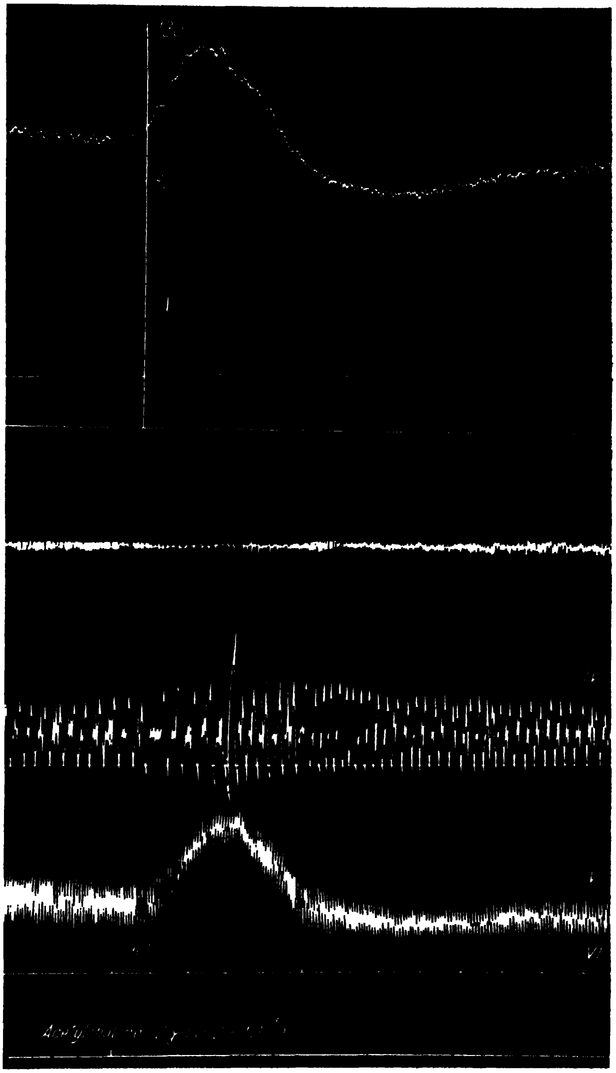

Fig. 69. Reflex effect produced on blood pressure by 0.000002 gr. of acetylcholine injected into vessels of intestinal loop isolated from general circulation, but with all nervous connections intact.

I—general blood pressure (mercury manometer); *II*—record of movements of isolated intestine; *III*—record of number of drops of fluid flowing out of vessels of perfused intestine; *IV*—record of respiration; *V*—record of blood pressure made by membrane manometer; *VI*—time intervals. Bottom line indicates injection of acetylcholine (after V. Chernigovsky).

There are reasons to believe that the chemoreceptors are located in the tissues of various organs, whereas the baroreceptors lie precisely in the vascular walls or in their immediate proximity (they probably include the pacinian corpuscles). However, the chemoreceptors are stimulated by various chemical agents circulating in the blood because most of them easily penetrate through the walls of the capillaries. In addition, any change in tissue metabolism of each organ leads to a change in the stimulation of its chemoreceptors which reflexly affects the circulation. Besides, a number of organs have other mechanoreceptors which are stimulated not by changes in the vascular pressure but by the stretching and relaxation of the smooth musculature and ligaments of these organs. Such are the mechanoreceptors of the oesophagus, the stomach, the intestines, the gall- and urinary bladders, the peritoneum, the pericardium and the meninges (D. Biryukov). The same organs (perhaps not all of them) have receptors of pain stimuli.

As the state of the body and of the organs in which these receptors are located vary the reaction caused by their stimulation may also change. Thus, for example, during a total cooling of the body stimulation of the interoceptors of the intestine does not lead to a rise, but to a drop in the blood pressure. The reflex reaction arising from the interoceptors of the female sex organs changes similarly during the various periods of the sexual cycle.

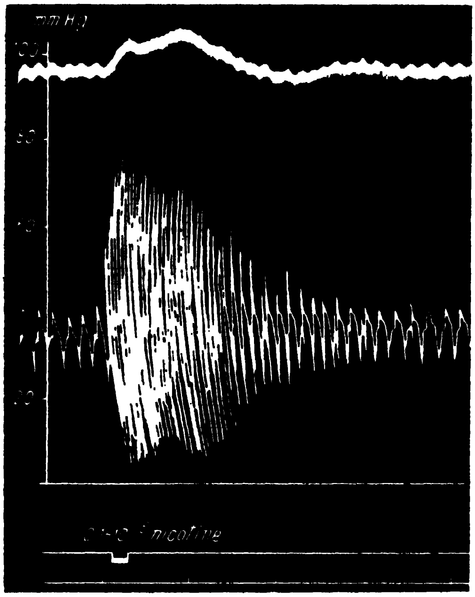

Fig. 70. Effect of stimulating chemoreceptors of bone marrow on blood pressure (upper record) and on respiration (second record from top).

Injection of 0.0001 mg. of nicotine (0.1 ml. solution diluted 1:10,000) into tibial marrow of the cat is marked on second line from bottom. Bottom line indicates time intervals (5 seconds) (after V. Chernigovsky and A. Yaroshevsky).

Changes (or pathological disorders) in metabolism of any organ affect the passage of metabolites formed in this organ into the blood. This creates the conditions for stimulating the chemoreceptors in the other organs of the body. Thus, circulation not only ensures all the processes of metabolism by delivering to the tissues the substances they consume and by removing the products of their metabolism; in addition to, and inseparably from this, circulation ensures the communication among the receptors of the various organs which affects the reflex regulation of circulation, respiration, etc.

The impulses arising in the baroreceptors, chemoreceptors and mechanoreceptors of the various small vessels continuously maintain (probably reflexly) the tone of the vasoconstrictor innervation and are at the same time in large measure responsible for the *redistribution* of the blood among different organs. Normally the blood is so redistributed that the arterioles of the vigorously functioning organs (for example, the muscles in muscular work, the skin at high temperature and the abdominal organs during the process of digestion) dilate and the capillaries open, whereas part of the arterioles and capillaries of the organs at rest become at the same time constricted or close.

Under normal conditions the cerebral cortex generally inhibits the reflex influences exerted by the interoceptors on circulation. This follows from the fact that in the experiment after the removal of the cerebral cortex stimulation of the interoceptors of the internal organs causes much greater reflex changes in the blood pressure than normally. Direct stimulation of the cerebral cortex by induction current usually leads to a decrease in the reflex reaction caused at the same time by stimulation of the interoceptors of the internal organs (Fig. 71).

Depending on the various states of the cerebral cortex its inhibiting influence on the vascular reflexes, which arise as a result of stimulation of different groups of interoceptors, may manifest itself differently sometimes, apparently, being replaced by a stimulating influence. We may assume that a decrease in the inhibiting influence of the cerebral cortex on the vascular reflexes, caused by stimulation of the interoceptors, leads to abnormally high blood pressure (especially if the effect of the reflex influences from the baroreceptors of the aortic and sino-carotid zone, which equalize the blood pressure, decreases at the same time). The impulses from the interoceptors which arise during abnormal states of the centres may, probably, reflexly lead to a number of pathological, so-called local, circulatory disorders (for example, in the extremities during endarteritis), i.e., to impairments of circulation in certain portions of the vascular system.

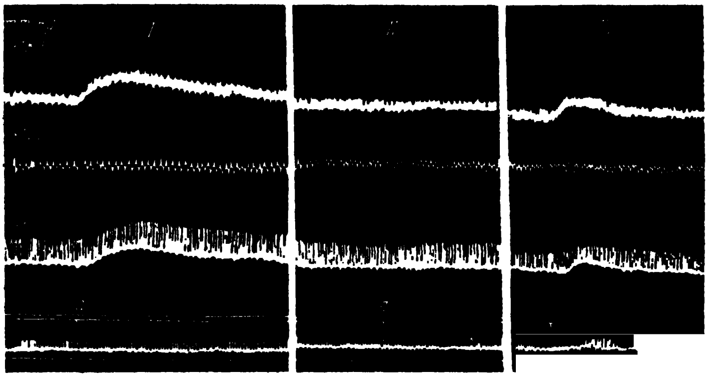

Fig. 71. Disappearance of reflex responses to stimulation of intestinal chemoreceptors under action of direct current cathode on parietal region of cerebral cortex.

From top to bottom: blood pressure (recorded by mercury manometer), respiration, record of blood pressure by membrane manometer, mark of stimulation. Letter *a* indicates addition of 0.5 solution of nicotine (10^{-4}) to liquid perfused through vessels of portion of intestine retaining its nervous connections with the body. Curve *I* was recorded before action of cathode on cortex, *II* —0.5 minutes after turning on current, *III* —30 minutes after cessation of its action. Bottom record indicates time intervals of 1 second (after V. Chernigovsky).

It is as yet impossible definitely to determine the significance of the receptors found by morphologists in all divisions of the venous system.

Effect of Stimulating the Exteroceptors on the Circulation

Considerable stimulation of the exteroceptors (by light, sound, thermal or traumatic agents) causes reflex constriction of the vessels as the primary response and (though not always) acceleration of cardiac activity. Plethysmographic studies of various organs (the extremities in man) shows that at the sudden sound or a strong thermal stimulation the blood pressure somewhat rises and the amount of the blood flowing through the extremity decreases (constriction of the vessels).

Constriction of the vessels and acceleration of the heart rate at the initial action of any specially applied stimuli, apparently form a component of the general orientation reflex occurring in response to a stimulus in the external environment, which formerly never or rarely acted on the given organism. In people with certain portions of the cerebral cortex of one hemisphere diseased (hemiplegia) stimulation of the skin on the opposite side of the body causes a weak and invariable reaction.

Stimulation of the exteroceptors, which in man does not lead to pain sensations or to variations in the heat exchange with the external environment, causes, when repeated, increasingly weaker reflex changes on the part of the heart and the vessels (as well as of respiration). The reaction to a "novelty," or what I. Pavlov designated as an orientation reflex or a "what is it?" reflex, is inhibited if the stimulation is repeated. If, however, a pain sensation arises or the skin is chilled in response to the stimulation of the exteroceptors the reflex constriction of the vessels and the acceleration of the heart rate caused by it do not decrease when the stimulation is repeated. A rise in blood pressure is the most characteristic reaction of the blood pressure to traumatic (pain) stimulation. However, under sustained and strong traumatic stimulation the reaction may be perverted, i.e., the vessels may dilate, sometimes resulting in a considerable drop in the blood pressure.

In response to stimulation of the skin by cold the vessels in the chilled region and in the corresponding parts of the body become reflexly constricted. The vascular reactions manifest themselves in man most markedly in response to chilling (or heating) of the portions of the skin which are usually exposed. An enormous role is played in this case by the natural conditioned reflexes developed on the basis of temperature influences.

Heating of the skin (and of the internal organs) leads to dilatation of the vessels. Thus, the blood flow through an arm immersed in water, heated to 42° C, may increase 6 to 8-fold compared with the blood flow observed in the skin acted upon by water, heated to 35° C.

Stimulation of the pain receptors often leads to dilatation of the vessels in the part of the body where the stimulated receptors are located and to simultaneous constriction of the vessels in other regions of the body. This is the so-called Lovén reflex.

Conditioned-Reflex and Complex-Reflex Regulation of Circulation

The mechanisms of circulatory regulation considered above are inborn and may also function after the removal of the cerebral cortex. But under normal conditions the cerebral cortex constantly regulates the activity of the circulatory system by influencing all the lower divisions of the central nervous system and by establishing the relations between all the functions of the body and the external environment.

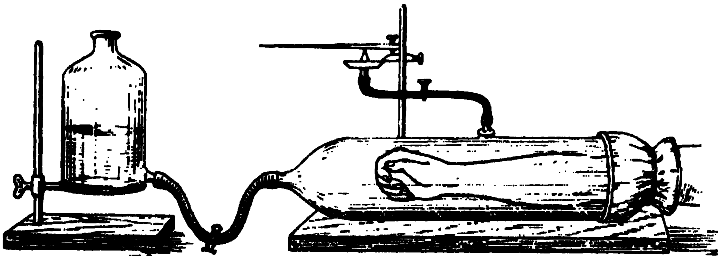

Fig. 72. Plethysmograph.

In studying normal circulatory regulation, especially in man, it is very important (in addition to studying the activity of the heart and the blood pressure) to record the value of the blood-filling of the extremities with the aid of a *plethysmograph.*

If the volume of the extremity placed in the plethysmograph increases the water is driven into the tube connected with the latter and the air in it compresses causing the rubber membrane covering the cavity of a Marey capsule, which is connected with this tube, to bulge. If the blood flows to and from the extremity at the same rate there will be no variation in the volume of the extremity. But since more blood flows into the arteries than out of them into the arterioles during systole the volume of the extremity during systole increases. This is shown by the pulse variations on the plethysmographic curve. Plethysmographic studies make it possible to record increases in the blood supply to the musculature during work and heating and decreases during cooling, respiratory variations, variations in the blood-filling of the extremities, etc.

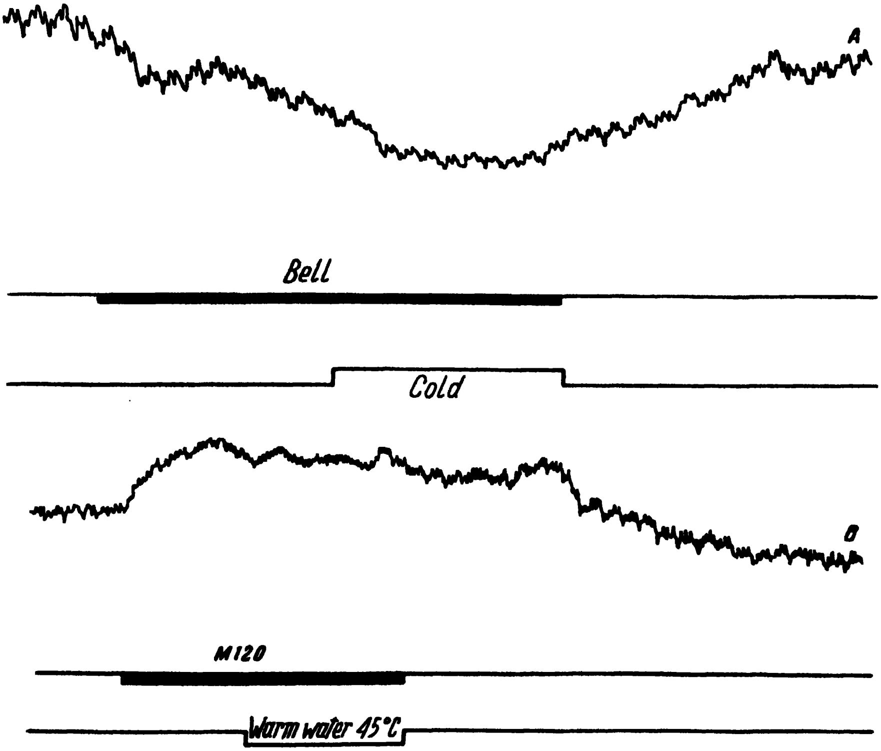

Fig. 73. Plethysmographic record of arm volume.

Upper record *(A)* shows constriction of vessels (decrease in arm volume revealed by lowered plethysmogram) at sound of bell previously repeatedly combined with action of cold and reinforced by stimulation with cold (mark "cold"). Lower record *(B)* shows dilatation of vessels (increase in arm volume revealed by rise in plethysmographic curve) at sound of metronome (M 120) previously combined several dozen times with warming the arm and reinforced by this warming (mark—warm water 45° C) (after A. Rogov).

Any stimulus coinciding with the action of an agent which causes an unconditioned vascular reflex becomes a conditioned stimulus causing the same vascular reaction. By accompanying the sound of a bell 50 to 80 times with the application of cold to the skin a marked constriction of the vessels is attained in the experiments on the effect of the bell alone (Fig. 73, top; the conditioned reflex begins to appear already after the aforesaid stimuli are combined 10 to 15 times). The agent preceding heat stimulation causes the typical dilatation of the vessels, which characterizes their reaction to heat stimulation (Fig. 73, bottom). The agents combined with the action of a pain stimulus cause (even if combined but few times) the same constriction of the vessels and acceleration of the heart rate as does the pain stimulation which they signalize.

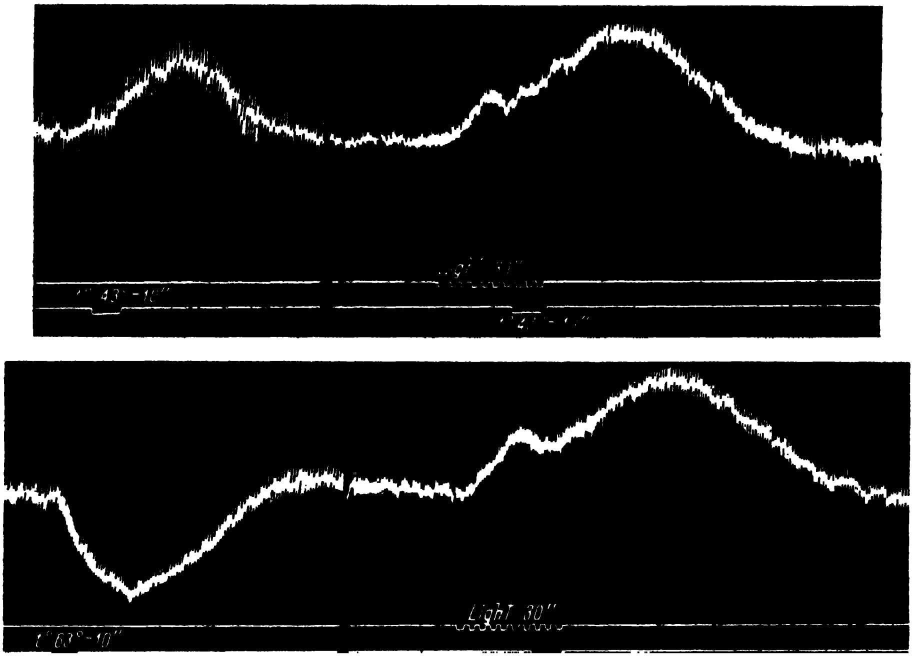

Fig. 74. Suppression of effect produced on vessels by unconditioned (pain) stimulus under influence of conditioned stimulus which causes opposite reaction of vessels.

Effect on blood-filling of arm (plethysmographic record): *top left*—of heat stimulation (mark: t° 43°-10″), *bottom left*—pain stimulation (mark: t° 63°-10″) produced by heating portion of skin by heat electrode. Thermal stimulation causes reflex dilatation of vessels (rise in curve), pain stimulation produces their reflex constriction (drop in curve). *Top right*—effect of conditioned stimulus (mark: light 30″) reinforced as usual by action of heat (mark: t° 43°-10″); *bottom right*—effect of pain stimulus (mark: t° 63°-10″) applied after signal of thermal stimulation (light) at moment when light stimulus is usually reinforced by heat. Unconditioned vascular reflex to pain stimulus (constriction of vessels) is completely suppressed (after A. Pshonik). In each illustration from top to bottom: plethysmographic record of arm volume, time of action of conditioned stimulus (intermittent flashes of bulb) and time of action of unconditioned stimulus.

The vascular conditioned reflexes are subject to all the laws established by the Pavlov school for cortical activity. Their development necessarily involves the cerebral cortex; in hemiplegia patients, in whom the haemorrhage impairs the connections of the cutaneous and motor analysers of the cortex of one hemisphere with the lower centres, the conditioned vascular reflexes are particularly disturbed on the side of the body opposite the focus of the disease. If not reinforced the vascular and cardiac conditioned reflexes are extinguished. They can also be inhibited by the action of extra stimuli (external inhibition).

Vascular conditioned reflexes may develop as conditioned reflexes of the second, third and higher orders in which a conditioned reflex is formed on the strength of the formerly developed conditioned reflexes rather than because it is reinforced by unconditioned reflexes. In man conditioned reflexes develop in response to verbal stimuli, words pronounced, heard and read (Chapter 65). Thus, if a bell is combined several times with a pain stimulus the words "I am going to ring" or showing a sign with the same words produces the same constriction of the vessels as does the sound of the bell or the pain stimulus signalized by it. People, subjected to these tests, later stated that such verbal stimulation sometimes produced a sensation of pain. Vascular reactions to verbal stimuli were also obtained in response to words which directly designated the action of the unconditioned stimulus; for example, a dilatation of the vessels in response to the words "I am turning on heat" and a constriction of the vessels in response to the words "I am making it cold" were regularly observed.

Observations made during studies of vascular conditioned reflexes show that their effect is often *stronger* than that of unconditioned stimuli. Normally all vascular reactions, like the changes in cardiac activity, always bear the stamp of cortical influences and occur as *complex-reflex* acts in which the conditioned and unconditioned nervous connections are knitted together. An unconditioned stimulus applied alone exerts a weaker influence on circulation than the same unconditioned reflex combined with its usual signals. It is precisely for this reason that the vascular reaction in response to exposing the trunk to the action of the wind, i.e., portions of the skin usually covered by clothes, is negligible, whereas the same exposure of the skin of the face to the wind (to an even weaker wind) is accompanied by a marked constriction of the vessels characteristic of the cooling effect usually produced by the action of the wind on man.

Since the influences of conditioned stimuli on the circulatory system dominate the conditioned reflex is reproduced even when an unconditioned stimulus, which in itself should produce a contrary effect, acts at the same time. Thus, if during the action of light transformed into a signal of heat stimulation by accompanying (reinforcing) it with heat we apply a pain stimulus (not very strong) instead of the heat the former does not produce the usual effect; dilatation of the vessels produced by the conditioned stimulus (light) continues, while constriction of the vessels characteristic of the pain stimulation does not take place.

It has been found that a verbal signal may also exert a stronger influence on the cardiovascular system than does an unconditioned stimulus. Thus, for example, if we apply a pain stimulus (not a very strong one, of course) at the words "I am turning on heat" we observe a dilatation of the vessels rather than their constriction despite the "unconditioned" action of the injurious agent. Under the circumstances the people studied experienced a sensation of the heat stimulation in accordance with the cortical signal of the second signal system (Chapter 65) rather than with the actual pain stimulus.

In people with a diseased cortex of one cerebral hemisphere (hemiplegia), as well as with functional disorders of the cerebral cortex, for example, due to starvation or stimulation, which upset the normal balance between excitation and inhibition (Chapter 61), the reaction of the vascular system to unconditioned stimuli changes: the reactions of the vessels to cold, pain and heat stimuli markedly decrease and become uniform. This also shows the great influence of cortical stimuli on the normal activity of the vascular system.

In fatigue, caused by physical or mental work, the vascular conditioned reflexes markedly weaken and sometimes even become distorted. In the latter case the agents constantly reinforced by, say, stimulation with cold may dilate rather than constrict the vessels. In fatigue the unconditioned vascular reflexes to heat and cold also change. The reflexes are weaker. This probably explains why it is so easy to catch cold when a tired body is exposed to the action of cold.

The cerebral cortex continuously influences the activity of all the lower central structures. This is manifest, in particular, in the constant inhibition of the excitation in the nuclei of the vagus by the cerebral cortex (A. Smirnov) and in the inhibition of the reflexes produced by stimulation of the interoceptors (p. 169); owing to this the changes in the activity of the cerebral cortex also affect the vascular system when the given changes are produced by signals which are not directly connected with the activity of the heart and of the vessels.

Normally the impulses from most of our interoceptors, including the receptors of the heart and the vessels, do not produce any definite sensations (for example, when a weak, barely felt mustard plaster is applied). They may, however, form temporary connections with the action of various agents of the external environment. Because of this a number of agents of the outside world acting simultaneously with certain stimuli of the interoceptors produce conditioned-reflex changes in the work of the internal organs (including the activity of the cardiovascular system) and influence the circulation. Here a continuous development of natural conditioned reflexes takes place. Thus, food stimuli combine with the stimuli of the interoceptors in the digestive tract and its vessels, which reflexly conditions an increased blood flow to the organs of the abdominal cavity. The odour and consumption of food are, therefore, necessary factors in the circulatory changes characteristic of digestion. The stimuli of the exteroceptors connected with the act of working similarly combine with the vascular, cardiac and respiratory reflexes, which arise during stimulation of the receptors of the musculature, etc.

Changes in the activity of the cerebral cortex may lead to pathological disorders of circulation. Suffice it to change in the experiment the nature of the reinforcement of the conditioned stimuli, for example, to replace the heat, which reinforces the effect of the bell, by cold, i.e., an agent which exerts a contrary reflex influence, to make the conditioned stimuli, whose action on the vessels is inhibited, produce negative vascular reflexes and the positive vascular reflexes to disappear. In this case wave-like variations in the blood-filling of the extremity appear depending on the variations in the excitation of the vasomotor centre and corresponding to the waves of arterial pressure of the third order.

CHAPTER 18

CIRCULATORY CHANGES IN VARIOUS STATES OF THE BODY

Interrelation of All Changes in the Circulatory System

Circulation supplies the tissues with nutritive substances and oxygen and removes the waste products (carbon dioxide and other substances) from the tissues. Any sustained increase in the activity of an organ is possible only if the blood flow to it is increased. If the circulation of an organ is impaired this organ can no longer function normally.

Thus, if the coronary vessels are affected the blood supply to the heart proves inadequate and cardiac activity is impaired. If the blood supply to the heart is not very much deranged the weakening in the work of the heart hardly manifests itself during muscular rest but clearly comes to the fore during muscular activity; even negligible muscular work produces a strong and protracted acceleration of the pulse, dyspnoea and pain in the region of the heart. The origin and significance of these symptoms are treated in detail in a course of pathological physiology.

Dilatation of the vascular channel in a small portion of the vascular system hardly influences circulation as a whole. Dilatation of the vessels in a large vascular region would immediately lead to a drop in the arterial pressure and, consequently, to a slowing down of the blood flow if these were not simultaneously attended by a) an increase in the activity of the heart, b) constriction of the vessels of the organs which at this time are in a state of rest, and c) emergence of the blood from the blood depots.

Effect of Muscular Work on Circulation

A number of reflexes evoked by the stimulation of the mechanoreceptors of the contracting muscles (as well as their tendons and ligaments), of the chemoreceptors of the muscular tissue and, probably, of the baroreceptors of the muscular vessels represent the inborn mechanism of circulatory regulation during muscular activity. These reflexes increase cardiac activity (the tone of the vagal fibres which inhibit the heart decreases and that of the cardiac accelerators increases). At the same time there is a reflex increase in the excitation of the vasomotor centre and an increased production of a number of metabolites (adenylic acid, acetylcholine, histamine, CO_2 and lactic acid). The increase in the concentration of these substances in the working muscles leads to dilatation of the capillaries and arterioles of these muscles. Meanwhile the excitation of the vasoconstrictor centre, which occurs reflexly during muscular activity, leads to constriction of the vessels only in the nonworking parts of the body, in the skin, in the abdominal organs and in the blood depots.

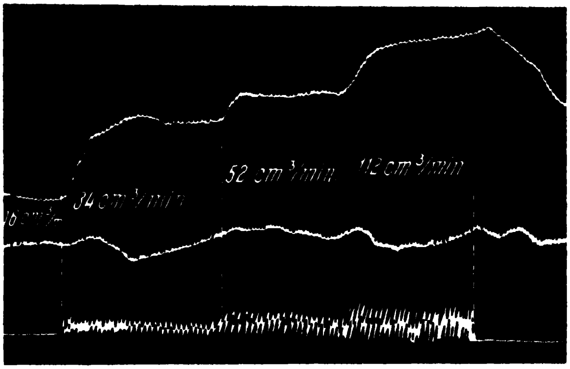

Fig. 75. Blood supply of muscle during work.

From top to bottom: curve of contraction of gastrocnemius muscle (contractions produced by direct stimulation of muscle by electric discharges); curve of blood pressure and curve showing rate of blood flow through femoral artery. Blood flow rate is indicated by figures. It is evident that the increase in the contraction of the gastrocnemius muscle is connected with the increase in the blood flow (after Rein).

During hard muscular work the concentration of lactic acid, hydrogen ions and carbon dioxide in the blood rises; the blood gives the muscles more oxygen than during rest. The change in the composition of the blood stimulates the chemoreceptors of the vessels and tissues distal to the active musculature. This gives rise to a number of new reflexes which alter circulation and respiration. The change in the composition of the blood, which bathes the central nervous system, also affects the state of the latter.

During muscular work circulation is normally regulated by cortical stimuli which arise as a result of a number of natural conditioned reflexes developing from the first months of life in response to the entire pattern of stimuli connected with various forms of muscular activity.

During hard muscular work the activity of the heart increases to the extent that its minute volume reaches 20 to 35 litres at a rate of 150 to 240 beats per minute and a stroke volume of 150 to 180 ml. Usually the arterial blood pressure does not rise sharply during muscular work because in addition to the constriction of the vessels of the resting organs, the increase in the work of the heart and the increase in the mass of the circulating blood, i.e., factors leading to a rise in the arterial pressure, there is an enormous increase in the vascular bed of the working muscles due to a dilatation of the arterioles and an increase in the number of open capillaries.

Circulatory Reactions to Changes in the Position of the Body

When the body is in a vertical position the blood flows by force of gravity to the organs of the abdominal cavity and especially to the lower extremities. In healthy people the systolic blood pressure does not change or drops only a few mm. Hg while the diastolic pressure slightly rises. In changing from the horizontal position to the vertical the pulse rate always increases owing to which the minute volume of the heart remains constant despite the fact that the beat (systolic) volume somewhat decreases. Maintenance of normal arterial blood pressure in a vertical position is possible because the decreased venous blood flow to the heart, which is due to the flow of blood to the legs, is compensated by a reflex constriction of the vessels of the abdominal cavity. It is probable that normally the natural conditioned reflexes, which arise because of the constant combination of the afferent impulses from the receptors of the muscles, contracting when the vertical position is assumed, with the reaction of the vasomotor centre condition the regulatory reaction (constriction of the vessels of the abdominal cavity and the acceleration of the heart rate) even before the change to the vertical position has actually occurred. When normal activity of the cerebral cortex is interrupted or disturbed, for example, in anaesthesia, the change to the vertical position causes a considerable drop in the arterial blood pressure.

Effect of Digestion and External Temperature on Circulation

During digestion the amount of blood flowing through the organs of the abdominal cavity increases by 30 to 50 per cent (this flow of blood to the organs of the abdominal cavity is probably responsible for the certain somnolence and desire for rest frequently noted in people after a substantial meal).

Any rise in the temperature of the surrounding environment causes an increased blood flow to the skin (a reddening of the skin in man). When a large portion of the body is heated a dilatation of the cutaneous vessels may cause a considerable drop in the blood pressure if it is not compensated by a constriction of the vessels of the abdominal organs, a draining of the blood depots and an increased activity of the heart.

Mechanism of Certain Circulatory Disorders

If the arterial blood pressure falls below 70 to 80 mm. Hg the blood supply to the central nervous system and to the heart is deranged; a substantial drop in the arterial blood pressure leads to rapid death if the reflex mechanisms do not equalize the pressure.

Effect of weakened cardiac activity. A considerable slowing down of the heart rate (to 30 or 20 and fewer beats per minute), as well as a substantial weakening of the cardiac contractions, always leads to a drop in the arterial blood pressure.

Losses of blood resulting in a decrease in the mass of the blood flowing in the circulatory system are responsible for a diminished blood flow to the heart and, consequently, for the fall in the blood pressure and for the disturbance in the nutrition of all organs, including the brain and the heart. If the loss of blood does not exceed 1/5 to 1/4 of the total amount of the blood the drop in blood pressure leads to a decrease in the stimulation of the receptors of the aortic-carotid zone which causes a reflex constriction of the vessels and a draining of the blood depots; owing to this the blood pressure may maintain the arterial pressure on a normal level. Subsequently, the fluids pass vigorously from the tissues into the blood. Disorders of the regulatory mechanisms greatly increase the danger of even small losses of blood. If the sympathetic nervous system is removed even a small loss of blood leads to death because of the irresistible fall of the blood pressure.

The phenomena of shock usually occur after abnormal stimulation of the vasoconstrictor centre and its motoneurons. This takes place during serious injuries always connected with stimulation of a large mass of receptors (for example, in crushed extremities, heavy injury to the abdominal cavity, considerable burn and stimulation of the receptors of the pleura and the nerve tracts which run in the region of the mediastinum). It is believed that the drop in blood pressure in shock is always preceded by a phase (sometimes very brief) of reflex stimulation of the vasomotor centre gradually replaced by inhibition, probably of a parabiotic nature (see Chapter 50).

The agents that stimulate the vasoconstrictor centre and alter the general state of the central nervous system often aid in the development of shock. Such is the effect of cooling and of a loss of blood (even a small loss). Typical shock can be produced not only by inflicting an injury on an animal or by deliberately stimulating a large number of afferent fibres (for example, by sustained electric stimulation of the sciatic nerves), but also by stimulating the interoceptors which are stimulated during blood losses, i.e., by stimulation which in the beginning reflexly excites the vasoconstrictor centre. If the loss of blood is so great that the arterial pressure is maintained at 30 to 40 mm. Hg for 1½ to 2 hours even the return of the entire extracted blood to the body after that raises the pressure only for a short time. The typical shock that develops is not due to any change in the conditions of haemodynamics caused by the loss of blood, but to the prolonged abnormal stimulation of the interoceptors and of the central nervous system, and to the insufficient blood supply to the higher divisions of the brain, which deranged the central innervation of the vessels.

The reaction of the higher divisions of the brain to the complex of stimuli, which cause shock, is of special importance in the development of the phenomena of shock. The cells of the cerebral cortex are, as Pavlov said, the most sensitive cells of the central nervous system and are, therefore, the first to be deeply affected when acted upon by especially strong impulses and to alter their functions as a result of abnormal conditions of activity. It has been found that a drop in the efficiency of the cortical cells due to inadequate nourishment fosters the development of shock. It has been shown (and this circumstance is made use of in practice) that the development of protective inhibition in the cerebral cortex, caused by administration of hypnotics, aids in preventing shock (E. Asratyan). It has also been shown that an injury inflicted during anaesthesia when the reactions of the cerebral cortex to afferent stimuli are weaker, and an injury to the regions of the body whose receptors were paralyzed by novocain (A. Vishnevsky) lead to shock much more seldom than an injury inflicted when the large hemispheres are in a normal state.

Hypertension. Sustained high blood pressure is called hypertension; this condition gradually leads to disorders of a number of functions of the body. High blood pressure adds a permanent extra load to the heart, alters the conditions of metabolic exchange between the blood and the tissues and causes additional stimulation of the baroreceptors which reflexly affects the nerve centres.

The reason for the rise in arterial pressure in hypertension is the sustained high tone of the smooth musculature of the arterioles.

Sustained high arterial pressure can be easily produced experimentally by denervation of the aortic and the sino-carotid zones. However, the rise in blood pressure after denervation of the aortic-carotid zone is partly due to the abnormally high heart rate caused by elimination of the impulses which increase the tone of the vagal centre. According to recent information (Chernigovsky) the sustained high arterial pressure produced by denervation of the aortic and carotid zones disappears after denervation of the kidneys. Experimental hypertension can also be produced by constriction of the afferent vessels of the kidneys which leads to increased production of *renin* (p. 159). But in the origin of *hypertension* in man neither of these mechanisms, which may lead to sustained high blood pressure, usually constitutes the primary factor. Many studies show that in the initial phases of hypertension no changes in the reaction to the stimulation of the sino-carotid zone nor any increase in the content of renin or hypertensin in the blood are noted.

In man hypertension mostly occurs after a period of extraordinarily vigorous activity of the higher divisions of the brain (G. Lang) especially when combined with poor nutrition. It has also been established experimentally that it is possible to produce a stable rise in blood pressure of animals by using "clashes" between the stimulatory and inhibitory processes in the cerebral cortex (Chapter 63) or by repeated action of superstrong stimuli. Changes in the functional state of the cerebral cortex lead to abnormally high excitation of the vasomotor centre (naturally, including in the idea of the vasomotor centre also the structures of the cerebral cortex involved in the regulation of the vascular tone). The abnormally strong stimulation of the vasoconstrictor neurons is, probably, due to a decrease in or a cessation of the inhibitory influence, which the cerebral cortex normally exerts on the vasoconstrictor centre. The stimuli, which normally produce a depressor effect, cause a rise in blood pressure when the central vasoconstrictor neurons are in a state of high excitability.

As a result of an increased excitation of the central vasoconstrictor apparatus the arterioles of a number of vascular regions, including the vessels of the kidneys, become constricted. This may lead to ischaemia of the kidneys and to an increased production of renin which together with the renin-activator of the plasma produces hypertensin, the vasoconstrictor substance. As a result the constriction of the vessels also increases under the influence of the humoral ("renal") factor; hypertension increases and becomes more stable.

Advanced hypertension, like all serious disorders of the circulatory system, gives rise to phenomena of a vicious circle when the insufficiency of circulation leads to an insufficient supply of blood to the brain and the entire innervational regulation of the heart and the vessels is impaired, which in its turn results in a still greater impairment of circulation and further disorders of its regulation.

CHAPTER 19

PECULIARITIES OF CIRCULATION IN CERTAIN VASCULAR REGIONS

Pulmonary Circulation

The blood pressure in the arteries of the pulmonary circuit is 1/5 to 1/6 that of the aorta. In the pulmonary artery it is 20 to 40 mm. Hg during systole and 4 to 15 mm. Hg during diastole. The mean pressure in the pulmonary artery is considered to be approximately 20 mm. Hg. Under normal conditions the blood flows through the pulmonary circuit in about

10 seconds. Normally the minute volume of the right heart equals the amount of blood flowing during the same period through the systemic circuit.

The lungs usually contain from 6 (during expiration) to 10 or 12 per cent (during a deep inspiration) of the total blood of the body. Since the capillaries and venules of the lungs are highly extensible the volume of the blood in the lungs increases when the flow of the blood to the left atrium is impeded. Overfilling with blood the pulmonary vessels can hold close to 1/5 of the total amount of the blood. This results in pulmonary congestion, in a rise in pressure in the minor circuit, especially in the pulmonary veins, and, owing to this, in a distention of the left heart. It is accompanied by an increase in the contractions of the left ventricle due to which the changes are in some measure equalized.

Coronary Circulation

The heart is nourished by the blood which flows along the two coronary arteries; the left coronary artery carries about 75 to 80 per cent of the blood coming to the vessels of the heart. The coronary arteries divide into smaller arteries, while the capillaries that arise from the latter entwine all of the muscular and nervous structures of the heart. The number of capillaries per unit of volume of the heart muscle is about twice the number of the capillaries in the skeletal muscles and increases during the functional hypertrophy of the heart. The greater part of the venous blood (60 to 70 per cent), which flows out of the capillaries, enters the right atrium through the coronary sinus; about 1/3 of the blood of the venous system of the heart enters small veins (thebesian veins).

The blood supply to the heart is peculiar in that during systole of the ventricles the flow of blood through the coronary arteries compressed by the contracting heart muscle temporarily decreases and less blood is, therefore, delivered to the heart tissues. Immediately following the end of the systole the blood supply to the heart increases (Fig. 76).

The higher the pressure in the aorta, everything else being equal, the more blood flows through the coronary vessels.

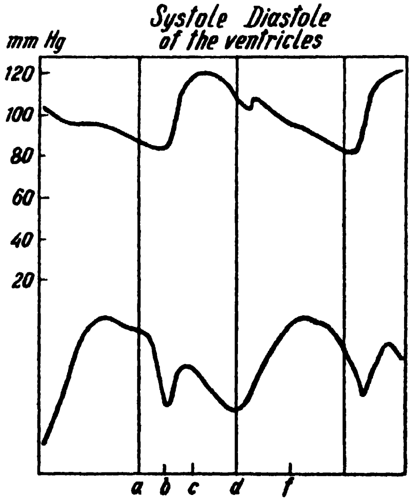

Fig. 76. Amount of blood (lower curve) flowing from coronary veins at different moments of the cardiac cycle, compared with the changes in the aorta (upper curve).

Between *a* and *b* - period of tension, between *b* and *c* - sharp rise in aortic pressure. Vertical lines show beginning and end of systole and diastole (after Ungers).

The myohaemoglobin contained in the heart muscle very easily gives off the oxygen with which it is combined. It is possible that during systole, when the flow of blood to the heart decreases, the splitting off of the oxygen from the myohaemoglobin plays an essential part in giving off the oxygen to the oxidized substratum. During diastole, when the heart is abundantly supplied with blood and an increased amount of oxygen is liberated by the blood, the myohaemoglobin recombines with oxygen.

The nervous regulation of the coronary vessels is singular in that here the sympathetic nerve fibres (the postganglionic fibres arising mainly from the stellate ganglion) and adrenalin usually dilate the coronary vessels. Stimulation of the sympathetic nerves or injection of adrenalin increases the coronary blood flow 2 to 3-fold. Contrariwise, *excitation of the vagal fibres leads to constriction of the coronary vessels*. The nerve cells whose axons are the fibres of the vagi which innervate the coronary vessels, are usually, apparently, in a state of certain excitation (the tone of the vasoconstrictor neurons innervating the coronary vessels).

The blood flowing through the coronary vessels is approximately 6 to 10 per cent of the minute volume of the heart. During muscular work, when the minute volume increases 8 to 10-fold, the blood flow through the coronary vessels, apparently, increases less markedly, only 3 to 4-fold, but much more oxygen of the blood is used in the cardiac capillaries.

The diseases of coronary circulation encountered clinically are coronary thrombosis (myocardial infarction) and angina pectoris (spasms of the coronary vessels).

Disorders of the normal blood supply to the heart very often give rise to keenest pains.

Cerebral Circulation

When insufficiently supplied with oxygen the nervous tissue and especially the cells of the higher divisions of the central nervous system cease functioning sooner than the cells of other organs. Compression of the vessels running to the human brain causes almost immediate loss of consciousness. A drop in the general blood pressure in the large arteries below 70 to 80 mm. Hg leads to an insufficient cerebral blood supply and to disorders of the cerebral function. In slight anaemia of the medulla oblongata the vasoconstrictor centre is stimulated, and this leads to a rise in blood pressure and to an increase in the blood flow to the brain.

Due to the constancy in the volume of the cranium the cerebral vessels show no pulsatory changes in the volume of the blood they contain. The blood flows along the cerebral vessels in a continuous stream, and the pulse waves in the cerebral arteries are suppressed.

Former investigators repeatedly described cerebral "pulsations" whose rhythm corresponded to the rhythm of the heart-beats. The studies conducted by Klosovsky have shown that these pulsations arise only after trepanation of the skull, i.e., creation of an opening in its osseous integuments.

Owing to the constancy in the volume of the cranium changes in the amount of blood contained in the cerebral vessels are possible only during corresponding changes either in the mass of the cerebral tissue (including the glia, etc.), or in the amount of the cerebrospinal fluid. If the blood flow to and from the brain increases to the same extent the rate of the blood flow to the brain may increase regardless of the total amount of blood which fills its vessels. Changes in the volume of the cerebrospinal fluid can hardly occur rapidly, and the increase in the amount of blood, which fills the cerebral vessels, is probably connected with a decrease in the volume of the cerebral tissue (including the glia and the intercellular substance) produced by a change in the state of its colloids. It is, therefore, probable that the nervous influences on the cerebral vessels are closely connected with the nervous reflex influences on the cerebral metabolism.

The blood is continuously redistributed in the brain because of the dilatation of the arterioles and capillaries in the portions of the cerebral cortex which are in a state of vigorous activity at the given moment and because of the simultaneous decrease in the lumina of the vessels in the portions of the cortex, which are at this time in a state of comparative rest (and, probably, in the portions of the cortex which are in a state of certain inhibition). B. Klosovsky observed that stimulation of the vestibular apparatus led to a dilatation of the vessels of the pia mater only in the parietal region of the cortex which receives the impulses from the stimulated receptors, whereas the vessels of the membrane of the occipital zone were at this time somewhat constricted. Contrariwise, illumination of the eyes leads to dilatation of the vessels in the occipital portion of the cerebral cortex.

PART IV

RESPIRATION

The process of respiration may be divided into:

1) *External (pulmonary* in higher animals) respiration, i. e., all gaseous exchanges between an animal organism and its environment which supplies oxygen to the blood from the environment and eliminates carbon dioxide from the blood.

2) *Transport of gases by the blood—oxygen* from the respiratory organs to the tissues and *carbon dioxide* from the tissues to the organs of respiration.

3) *Internal* or *tissue* respiration, which includes all forms of oxygen consumption by the cells and production of carbon dioxide in the cells as a result of the oxidative processes which lead to liberation of energy.

CHAPTER 20

PULMONARY RESPIRATION

Development of Respiratory Organs

Structure. The organs of respiration of various animals differ in structure, but all have a large surface of contact with the external environment and are abundantly supplied with blood vessels, which ensure gaseous exchange between the external environment and the blood. The significance of the skin as a surface through which gases may be exchanged diminishes in the process of evolution because of the development of the corneal layer of epithelium which is almost impermeable to gases.

Aquatic animals breathe through gills which are outgrowths of the body surface or (as in fish) of the anterior division of the gut. Insects respire through a peculiar system of air passages which reach all tissues.

The entire system of gas transport by the body fluids also changes in the course of phylogenetic development. In the lower organisms this process is confined to transport of gases dissolved in the blood; during subsequent evolution oxygen chemically combines with the respiratory haemoglobin pigments. The respiratory pigment of invertebrates is dissolved in the plasma; in vertebrates it is found only in the blood corpuscles. Changes in the mechanism of oxygen transportation by the blood also affect the conditions of carbon dioxide transport. The end results of this evolutionary development of the functions of the blood are, firstly, the capacity to transport considerable amounts of gases by a restricted quantity of fluid and, secondly, the carrying out of all the chemical processes of gas assimilation and elimination without marked shifts in the physicochemical properties of the blood (hydrogen ion concentration and osmotic pressure).

In mammals the entire gaseous exchange with the environment is actually effected through the surface of the lungs with no more than

1-1.5 per cent of the consumed oxygen being absorbed through the skin and the digestive tract.

Anatomy of the lungs. The lungs consist of epithelial tissue, rich in elastic fibres, which forms a tremendous number of microscopic air-sacs—the alveoli. The very thin walls of the alveoli are surrounded by capillaries of the pulmonary artery. There are hundreds of millions of these alveoli in the lungs so that despite the negligible size of each individual alveolus their total surface in man is from 60 to 120 m.^{2}. The alveolar cavities come in contact with the atmospheric air through the bronchioles, bronchi, trachea and nasopharynx.

The exchange of gases between the blood and the air occurs only in the alveoli and, possibly, in the terminal bronchioles (so-called respiratory bronchioles). The bronchioles, bronchi, trachea and nasopharynx are nothing but air passages through which the cavities of the alveoli communicate with the atmosphere. These air-carrying channels in a human adult have a volume of 120 to 180 ml., while the volume of air filling the alveoli is usually 2 to 3 litres.

Mechanism of Lung-Volume Changes During Respiratory Movements

Pulmonary breathing results from the changes in the volume of the lungs conditioned by the respiratory movements of the thorax. The volume of the lungs increases during each inspiration owing to an enlargement of the thoracic cavity produced by contractions of a number of skeletal muscles. The pressure of the air in the lungs falls below that of the atmospheric air and the latter is sucked into the lungs. During an expiration the volume of the lungs diminishes because of a decrease in the size of the thoracic cavity; the air pressure in the lungs rises by 20 to 40 mm. H_2O above that of the atmosphere and the pulmonary air is forced out.

The lungs passively follow all changes in the configuration and volume of the thorax. This dependence of the volume of the lungs on the size of the thoracic cavity is conditioned by the extensibility of the lungs and the anatomic relations in the thorax.

Extensibility and elasticity of the lungs. The lungs contain a large amount of elastic tissue and are, therefore, very extensible and elastic. This can easily be observed if we compress the trachea and open the thorax. The lungs appear as large pink-coloured bags. With the opening of the trachea the lungs at once collapse, the air leaves them and they now look like small grey structures lying on the dorsal wall of the thorax. If air is pumped into the lungs from bellows connected with the trachea they will greatly distend and protrude from the open thoracic cavity.

The lungs will always distend, like any hollow body with extensible walls, when the air pressure on their internal surface is higher than that on their external surface. In other words, distention of the lungs requires a *difference in pressures* on their inner and outer walls. This difference in pressures is the force necessary to overcome the resiliency of the pulmonary tissue which may be designated as the *elastic pull of the lungs.* Its value is easily determined by measuring the pressure required to distend the lungs with air pumped into them by bellows.

A T-tube connected with bellows and a manometer is inserted in the trachea of the animal with an open thorax. If the atmospheric pressure acting on the external surface of the lungs in the open thorax is 760 mm. Hg we can increase the internal pressure in them, say, to 765 mm. by pumping air into them. The excess pressure exerted on the internal walls of the lungs will be the force to overcome their elastic recoil and to distend them. The greater the difference between the air pressure inside and outside the lungs the more they will distend. It is clear that this difference between the external and internal pressure can be made to vary within the same limits either by increasing the internal pressure or by a proportional decrease of the external atmospheric pressure.

Donders' experiment. Donders' experiment serves to illustrate this principle. The device consists of a glass jar whose bottom is replaced by a rubber membrane. The lungs inside this vessel communicate with the external air through a tube inserted in the trachea, and held mainly by a stopper which hermetically seals the vessel (Fig. 77). The lungs thus communicate with the atmosphere, whereas the space that surrounds them does not. A pull on the rubber membrane of the vessel increases the volume of the latter, while the air in the space that surrounds the lungs rarefies and its pressure drops in relation to the atmosphere. The atmospheric pressure acts on the internal surface of the lungs through the tube inserted into the trachea. This results in a difference between the pressure of the atmosphere and that of the rarefied air in the space surrounding the lungs. The difference in the pressures distends the lungs when the bottom of the vessel in Donders' model is pulled on.

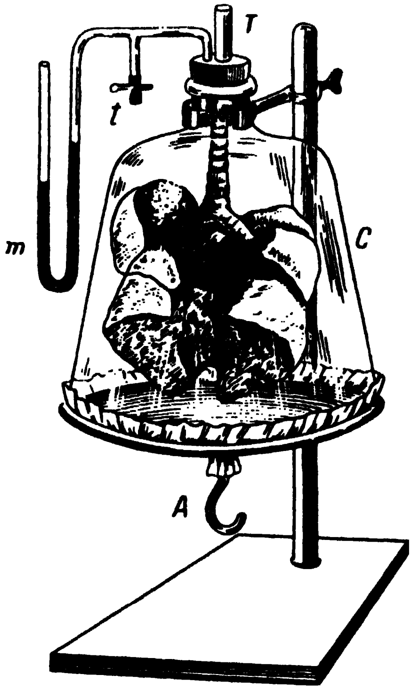

Fig. 77. Donders' model (explanation in text).

The conditions determining the changes in the volume of the lungs during the act of respiration physically resemble the relations imitated in Donders' experiment, since in both cases the distention of the lungs depends on the lowering of the pressure in the space surrounding them. It should be remembered, however, that normally there is no air around the lungs.

Negative pressure in the pleural cavities surrounding the lungs and its variations during inspiration and expiration. The lungs are in the thoracic cavity which is normally always hermetically sealed. The outer surface of the lungs is entirely invested in the *visceral pleura* which forms a single whole with the former. The inner wall of the thorax, the diaphragm and the organs of the mediastinum are covered with the *parietal pleura.* The pleurae are lubricated by a small amount of serous fluid which decreases their friction during respiratory movements. Between the visceral and parietal pleurae there is a narrow capillary slit which is frequently wrongly termed the pleural cavity, but which should rather be designated as the interpleural slit or virtual interpleural space.

Thus, *the lungs are in a hermetically sealed thorax and are surrounded by the pleurae with an interpleural capillary slit which does not communicate with the atmosphere and does not contain any air.* The atmospheric pressure, therefore, exerts unilateral action on the inner surface of the lungs and presses with all its force the lungs and visceral pleura to the walls of the thoracic cavity covered with the parietal pleura. The atmospheric pressure acting in the above manner on the inner wall of the lungs is scores of times as great as their elastic recoil distended as they may be. Because of this, *whatever the volume of the thoracic cavity, the lungs always fill its entire space not taken up by other organs.* During each inspiration the contractions of the skeletal muscles in the walls of the thorax (external intercostals), the diaphragm and others increase the capacity of the thoracic cavity in the vertical, transverse and saggital diameters.

During inspiration the contracting muscles of the thoracic walls pull the parietal pleura away from the lungs with their visceral pleura. However, the pleurae cannot be separated because atmospheric pressure always presses the lungs with the visceral pleura to the parietal pleura, i. e., to the walls of the thoracic cavity. But the pull produced by the contraction of the muscles, which expand the thorax, leads to a fall in pressure* in the interpleural slit.

Here we have about the same thing that happens when we try to lift a half-ton weight, which lies on a platform, by an effort of our muscles that develop a pull of, say, 50 kg. (it goes without saying that the man lifting the weight must not stand on the scale platform). By developing a 50-kg. effort the man will, naturally, be unable to lift the half-ton weight, but at the moment this traction is applied to the weight its pressure on the platform of the scales will not be 500 kg., but 500 kg. minus 50 kg., i.e., 450 kg.

The value of this drop in pressure is determined by the degree of distention of the lungs at any particular moment in the act of respiration.

Let us see what happens when the lungs no longer distend (after completion of an inspiration) or do not contract (during the pause following the expiration). An elastic body is in a state of constant tension only when the force which stretches it is equal in magnitude, but of opposite direction, to the forces of recoil which tend to contract it. Therefore, while the lungs do not distend and do not collapse the difference in pressures on their external and internal walls, i. e., the excess pressure exerted on the inner wall, exactly balances their elastic recoil. But the pressure exerted on the inner wall of the lungs through the air passages is an atmospheric pressure which exists at a given time and at a given point of the earth's surface. On the other hand, the pressure on the outer wall of the lungs is a pressure existing at a given period in the hermetically sealed pleural cavity. It follows that *the pressure in the slit-like interpleural space surrounding the lungs corresponds to the atmospheric pressure minus the pressure developed by the elastic recoil of the lungs; and, contrariwise, the elastic recoil of the lungs corresponds to the difference between the atmospheric pressure and the pressure existing in the interpleural slit.*

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* In dealing with the correlations of the pressure in the lungs and in the interpleural space surrounding them it should be borne in mind that in the latter it is a pressure exerted in a liquid which fills this space and is transmitted to the visceral pleura.

The elastic recoil of the lungs can be directly measured as pressure developed in the collapsing lungs when their distention ceases. The value of the elastic recoil in animals can be measured by opening the thoracic cavity and the parietal pleura and connecting the trachea with a manometer beforehand. In this case atmospheric pressure will act similarly on both the inner and outer walls of the lungs; due to their elasticity the lungs will collapse. If the trachea is stopped up the air will not be able to leave the lungs after the thoracic cavity is opened and the pressure developed by the elastic walls of the collapsing lungs is communicated to the manometer connected with the trachea.

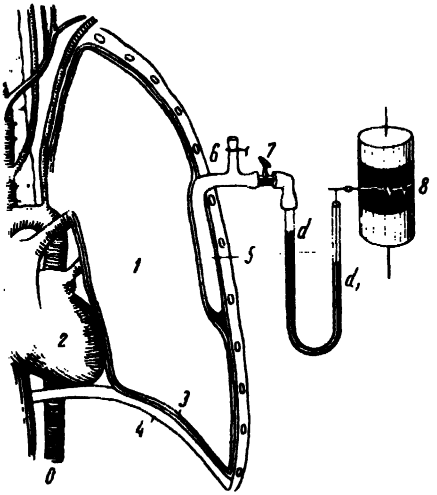

Fig. 78. Measuring negative pressure (schematic).

1—left lung; 2—heart; 3—pleura; 4—diaph
5—needle in pleural cavity; 6—Mo
7—tap; d and d_1—mercury levels in
8—kymograph on which pressure v
pleural cavity during inspiration an
can be recorded.

The deeper the inspiration, the more the lungs distend and the greater, therefore, the total elastic recoil developed by their distended walls. With maximum inspiratory effort the difference in pressures reaches 10 to 15 mm. Hg.

The interpleural pressure in man may be measured by pleural puncture often used clinically in pulmonary and pleural diseases. A hollow needle connected with a manometer (Fig. 78) is introduced into one of the intercostal spaces. When the point of the needle is in the interpleural space the fluid in the limb of the manometer connected with the needle rises. This proves that the pressure in the interpleural space is always lower than atmospheric.

It has been established that the pressure in the interpleural space is:

1.5 to 2 mm. Hg lower than atmospheric at the end of maximal expiration;

2 to 3 mm. Hg lower than atmospheric at the end of an ordinary expiration;

4 to 5 mm. Hg lower than atmospheric at the end of an ordinary inspiration;

10 to 15 mm. Hg lower than atmospheric at the end of maximum inspiration.

If we take the atmospheric pressure at a given moment and at a given point of the earth's surface as zero we may conditionally designate all values below atmospheric pressure as *negative*.

In this sense the pressure in the interpleural space is not infrequently designated as negative. The *value of the negative pressure is the difference between the atmospheric pressure at the given time and at the given point on the earth's surface and the pressure in the interpleural space surrounding the lungs.* When it is said, for example, that the negative pressure in this space corresponds to 8 mm. Hg and the atmospheric pressure is, say, 752 mm., it means that the absolute value of the pressure between the pleurae equals 752 minus 8, i.e., 744 mm. Hg.

Negative pressure in the interpleural space during maximum expiration. The persistence of some distention in the lungs and, consequently, the presence of negative pressure in the interpleural space even after maximum expiration is due to the fact that during the first months of life the walls of the thorax grow faster than the lungs and, therefore, soon after birth the capacity of the thoracic cavity is greater even after the deepest expiration than the volume the collapsed lungs would have. The lungs cannot but follow the slowly occurring changes in the volume of the thorax during its growth for the same reason that they cannot help following all the changes in the capacity of the thoracic cavity during respiratory movements. Through the air passages atmospheric pressure always presses the lungs with their visceral pleura against the parietal pleura, and the lungs cannot therefore move away from the chest walls when the volume of the thoracic cavity increases with the growth of the body. This is why the lungs do not fully collapse even after maximum expiration when there is still 1 to 1.5 litres of air left in them. The pressure in the pleural cavity remains at 1.5 to 2 mm. Hg below atmospheric.

Significance of negative pressure in the thoracic cavity. The thoracic cavity (outside the interpleural space) contains part of the oesophagus, the heart encased in the pericardium, all the pulmonary vessels, the initial portion of the aorta with the branches of the vessels arising from it, the superior vena cava, a portion of the inferior vena cava and the vessels emptying into them. Acting on the parietal pleura the elastic recoil of the lungs is transmitted to all the organs contained in the thoracic cavity. The negative pressure created by this recoil of the lungs hardly affects the blood pressure in the arteries and in the ventricles of the heart. But recoil essentially affects the return of the venous blood to the heart because it dilates the thin walls of the veins. The lower the pressure in the large veins of the thoracic cavity the greater the difference between the pressures of the blood in the capillaries and in the veins near the heart.

Let us assume, for example, that the blood flows from the capillaries into the veins under a pressure of 150 mm. H_2O. In the large veins of the thoracic cavity the pressure during inspiration is from 60 to 80 mm. H_2O below atmospheric; this will increase the difference between the blood pressure in the capillaries and that in the venae cavae from 210 to 230 mm. H_2O. With maximum inspiration the pressure in the thoracic cavity drops even from 130 to 180 mm. H_2O below atmospheric, which increases the difference between the pressures in the capillaries and the veins emptying into the heart still more. The negative pressure in the thoracic cavity aspirates the venous blood to the heart.

Subatmospheric pressure is also communicated to the large veins near the thoracic cavity: the jugular vein in the lower portion of the neck, the brachial vein under the clavicle and the system of the vertebral veins. We can thus understand the danger of air bubbles being aspirated into these veins (embolism) if they are injured during an operation.

Experiments of Müller and Valsalva. If an inspiration is attempted with mouth and nose closed, the chest and, consequently, the lungs expand, though to a lesser extent than with an ordinary inspiration of equal force. The pressure of the air contained in the lungs drops by 50 to 60 mm. H_2O below atmospheric. The pressure in the pleural cavity, being as usual lower than the air pressure in the alveoli by the value of the elastic recoil of the lungs turns out to be below atmospheric by 53 to 63 mm. H_2O

(the elastic recoil of the lungs not accompanied by a passage of air into them during an inspiration is approximately 3 mm. because the lungs cannot greatly expand in this case. Thus an inspiration with the nose and mouth shut (Müller's experiment) sharply reduces the pressure in the space surrounding the lungs.

Contrary to Müller's experiment that of *Valsalva* consists of a deep expiration with the nose and mouth shut. In this case the air pressure in the lungs rises from 40 to 100 mm. H_2O above atmospheric. Though the pressure in the thoracic cavity remains as usual lower than that in the lungs it rises 38 to 98 mm. H_2O above atmospheric pressure. The flow of the blood to the heart is impeded because the pressure at the point where the venae cavae enter the atria is excessively high. The veins of the neck and face swell. In cardiac insufficiency the resistance developed in the pulmonary vessels cannot be overcome and the circulatory disturbance results in syncope.

Pneumothorax

Pneumothorax refers to the condition in which air enters the interpleural space through the parietal pleura following a penetrating wound of the thoracic (and sometimes the abdominal) cavity or because of a tear in the lungs and the visceral pleura. If the interpleural space freely communicates with the atmosphere (open pneumothorax) the pressure between the pleurae becomes equal to atmospheric. In this case there is no more difference between the pressures acting on the inner and outer walls of the lungs and the lungs inevitably collapse because of their own elastic recoil.

Open pneumothorax can easily be observed in an animal if we widely open its thoracic cavity and parietal pleura. Despite the vigorous respiratory movements (they are apparent from the movement of the ends of the resected ribs and of the diaphragm) the lungs do not fill with air and remain collapsed; death from asphyxia soon ensues.

In bilateral open pneumothorax the animal's life can be saved only by artificial respiration, i.e., by forcing air into the lungs with bellows or a special pump. In this case the lungs are distended by raising the interpulmonary pressure above atmospheric by the value necessary to overcome the elastic recoil of the distending lungs. Such artificial respiration makes it possible to perform operations in which both sides of the thoracic cavity are opened (in man the interpleural spaces do not communicate with one another and a one-sided, even full, pneumothorax does not lead to asphyxia).

If the opening which produced the pneumothorax is closed, the air that entered the interpleural space is sealed off from the atmosphere and during inspiratory expansion of the thoracic cavity the air pressure in the interpleural space will diminish (only the air in this space should be sealed off from the atmosphere during expiratory effort). The lungs will expand again during inspiration, but the volume of their maximum possible distention will be reduced by the volume of the air remaining in the pleural cavity after the aperture which caused the pneumothorax is closed. The same decrease in the distention of the lungs occurs during inspirations in artificial, closed pneumothorax induced in tubercular patients for therapeutic purposes, i.e., for reducing the respiratory excursions of the affected lung. In this case the air is pumped into the interpleural space through a puncture in the thoracic wall and the pulmonary distention is reduced to a degree corresponding to the volume of the air (or nitrogen) introduced into the pleural cavity. It is clear that the lungs likewise distend less during inspirations if there is an accumulation of exudate or pus between the pleurae.

Mechanism of Respiratory Movements

Pulmonary respiration is effected by the action of a number of skeletal muscles whose contractions change the capacity of the thoracic cavity.

Role of the diaphragm. The diaphragm divides the thoracic and abdominal cavities; it has the form of a double dome pointed towards the lungs.

When the muscular fibres of the diaphragm contract its domes descend, while its lateral surface moves away from the thorax (Fig. 79), the central tendinous part lowering but little. A plane drawn through the upper points of the diaphragm during expiration lies on the level of the fourth and fifth ribs, while during inspiration the flattened diaphragmatic domes come down 3 to 4 cm. to the level of the seventh and eighth ribs. The contraction of the diaphragm increases the volume of the thoracic cavity vertically, a one cm. descent of the diaphragm increases the capacity of the thoracic cavity by approximately 250 to 300 ml.

When the diaphragm descends during contraction it presses on the abdominal organs pushing them down and forward and making the abdominal wall protrude.

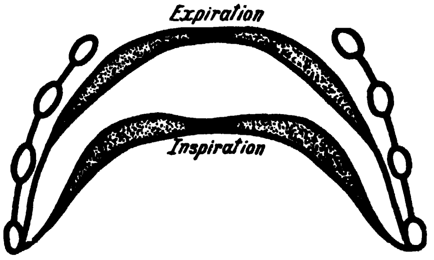

Fig. 79. Position of diaphragm during inspiration and expiration (after Norris and Landis).

The diaphragm is innervated by a pair of diaphragmatic nerves (phrenic nerves). The fibres forming these nerves are axons of the nerve cells, located in the anterior horns of the third to fifth cervical segments of the spinal cord, and leaving them with the third to fifth anterior cervical spinal roots.

Position of ribs and sternum in inspiration and expiration. Each rib is articulated with a vertebra at two points: its head articulates with the body of the vertebra and the tubercle with the transverse process of the vertebra. During inspiration the costal arches rise and the sternum moves forward. In expiration the ring formed by each pair of ribs and the sternum slants obliquely downward. During inspiration the ribs turn somewhat around the axis, which runs through the points of articulation of the ribs with the spine and each rib rises (Fig. 80). During this movement each costal arch (from the third to the seventh) rises more than the one above it. Because of this the sternum moves forward and somewhat upward so that during an inspiration the size of the thorax increases in its saggital diameter. At the same time each rib rotates its inferior surface slightly outward which also adds to the expansion of the thoracic cavity.

During inspiration the movements of the ribs are due mainly to the contraction of the external intercostal muscles which run downward and forward from a rib above to the rib below.

Deep breathing brings into play the *scalenus anticus* and most of the muscles of the trunk (which inclines somewhat to the back as the shoulders are raised).

Mechanism of expiration. When the contraction of the muscles responsible for the inspiration ceases the muscles relax and resume the position they occupied before the inspiration. The diaphragm rises and the ribs descend. This reduces the volume of the thorax; in normal breathing expiration is passive and is due to the relaxation of the muscles whose contraction caused the inspiratory effort.

Studies of the bio-electric currents in the respiratory muscles have shown that the muscles whose contraction reduces the volume of the thorax (chiefly the interna intercostal muscles) are in a state of weak tonic contraction during the interval between the respiratory movements. During inspiration the tension of these muscles decreases, but after the inspiration the muscles which lower the ribs and reduce the volume of the thorax resume their tone. This aids in the deflation of the thorax. In deep breathing these muscles contract strongly during expiration. In this case the expiration becomes active and as it ends the volume of the lungs is much smaller than in normal expiration. A forced expiration brings into play a number of other muscle groups, in particular, the muscles of the abdominal wall which by their contraction press the abdominal viscera upward and thus help the ascent of the diaphragm.

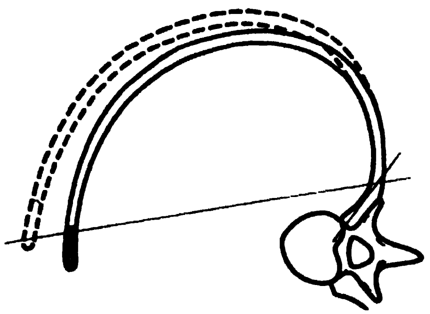
Fig. 80. Position of rib during inspiration (dotted line) and expiration (continuous line).

Abdominal and thoracic types of breathing. Under normal conditions breathing results from the movements of both the diaphragm and the ribs; the first mechanism (so-called abdominal type of breathing) is somewhat more frequent in men, while costal respiration (so-called thoracic type of breathing) plays a relatively greater part in women. The type of breathing may vary with posture, fixation of the shoulder girdle or abdominal wall and with disease (for example, in pleurisy, pneumonia or painful conditions in the abdominal viscera), and may be effected mainly by the movements of the diaphragm in one case or by the movements of the ribs and sternum in another.

Ventilation of various portions of the lungs. In normal respiration the lower two-thirds of the lungs distend most. The region where the bronchi and the vessels enter the lungs and the part close to the dorsal surface of the thorax hardly distend at all. The apices of the lungs also distend very little, i.e., are very poorly ventilated, in normal breathing. Here the air is renewed mainly because of the change in pressure in the more mobile parts of the lungs.

Not all the alveoli are involved in normal respiration simultaneously; some of them remain deflated. They distend during reinforced breathing (for example, during muscular work and under the action of rarefied air). This is apparent, in particular, from the fact that the capacity of the human lungs increases during muscular work. Thus, on a low level of activity, in the lungs, like in the capillaries of the vascular system, the "functional units" are switched on alternately.

A record of the respiratory movements may be obtained by connecting either a pneumograph (Fig. 81-*a*) to the walls of the thoracic or abdominal cavities, or Marey's capsule to a tube encircling the thorax (Fig. 81-*b*). The movements of the thorax or the abdominal wall are registered in the former case and the pressure changes in the air passages during inspiration and expiration in the latter. A *pneumogram* thus recorded is shown in Fig. 90.

Pulmonary ventilation, i.e., the amount of air breathed in and out per minute,* is recorded by special gasometers.

At rest man usually makes 14 to 18 respiratory movements (inspirations and expirations) per minute, each time inspiring and expiring about 0.4 to 0.6 litres of air. The same degree of pulmonary ventilation may be achieved with a different rate and correspondingly changed depth of breathing. At rest and under normal conditions the respiratory rate is never lower than 8 nor higher than 20 per minute. During any appreciable increase in basal metabolism (consumption of oxygen and elimination of carbon dioxide) pulmonary ventilation also increases, with the volume of each inspiration and expiration increasing more than the respiratory rate. During very hard physical work pulmonary ventilation may rise from 90 to 120 (and more) litres per minute, the volume of each inspiration and expiration reaching 2.5 to 3.5 litres (5 to 7 times the volume at rest) and the rate increasing from 25 to 40 times per minute (only 50 to 100 per cent). Certain pathological conditions of the lungs are accompanied by rapid and shallow

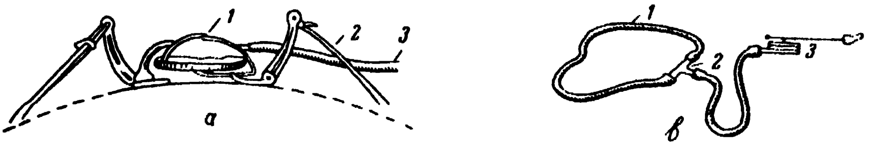

Fig. 81.

Left—pneumograph, somewhat modified Marey's capsule *(1)* fastened on thoracic wall by tape *(2)* so that with each inspiration stud of capsule presses on its rubber membrane; pressure variations in the pneumograph are propagated through tube *(3)* to recording device.
Right—pneumograph consisting of rubber tube placed around thorax. During inspiration rubber tube *(1)* stretches, during expiration it contracts; variations in pressure of air contained in tube are recorded through T-tube *(2)* by Marey's capsule *(3)* connected with tube.

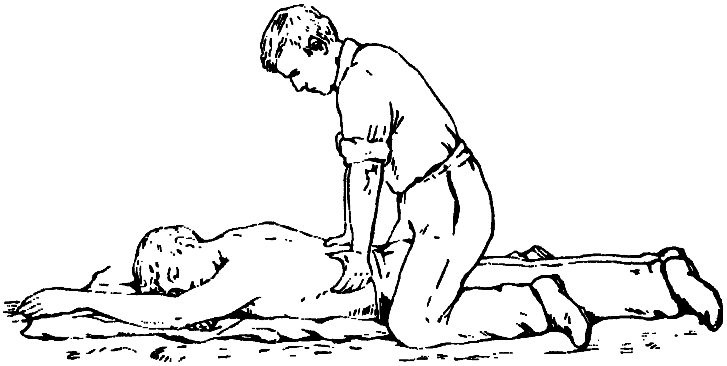

Fig. 82. Schafer's method of artificial respiration.

Pressure on thorax drives air out of lungs (expiration); when pressure on thorax is released chest expands and air enters lungs (inspiration).

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* The amount of inspired air is somewhat greater than that of the expired air since the volume of oxygen consumed by the organism at muscular rest is usually 1/6 to 1/5 larger than the exhaled CO_2; the volume of nitrogen remains the same.

breathing and not infrequently by a subjective sensation of asphyxia (dyspnoea, as observed in heart disease, pneumonia and other diseases).

Artificial respiration. In paralysis of the respiratory muscles (paralysis of the respiratory centre) the lungs can be supplied with air only through so-called artificial respiration. In a number of cases (in different forms of asphyxiation, drowning, electric shock, deep anaesthesia or poisoning by certain gases) when respiration is paralyzed, but the heart still works, artificial respiration may save the life because it ensures gaseous exchange for the time necessary to restore the activity of the respiratory centre (there have been cases when normal breathing was restored after 4 to 6 hours of artificial respiration).

Artificial respiration consists in compressing the thorax and forcing the air out of the lungs. When the compression of the thorax ceases it resumes its original shape because of the elasticity of the tissues of its walls and atmospheric air enters the lungs (Fig. 82). Unlike normal breathing the inspiration in this case is passive, while the expiration is a result of artificial compression of the thorax. Special contrivances are sometimes used in artificial respiration. The latter holds particularly true in protracted respiratory paralysis caused by poliomyelitis, in operations connected with opening the thorax or in operations in which the preparations used paralyze the skeletal muscles and enable the surgeon to operate while it is fully relaxed.

Residual, Supplemental, Tidal and Complemental Air. Vital Capacity of the Lungs

Some air remains in the lungs even after forced expiration. This is due to the fact that the lungs are somewhat distended even then. The air contained in the lungs after maximal expiration is called the *residual* air. Its volume equals 1,000 to 1,500 ml. The volume of residual air increases with age and reaches 2 to 2.5 litres in the aged people.

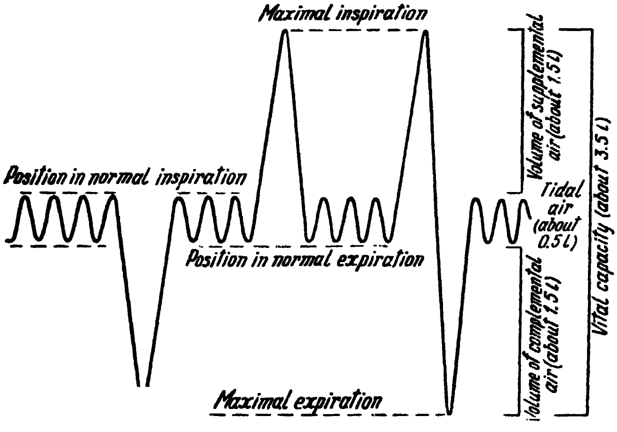
Maximal inspiration
Position in normal inspiration
Position in normal expiration
Maximal expiration
Volume of supplemental air (about 1.5 l)
Tidal air (about 0.5 l)
Volume of complemental air (about 1.5 l)
Vital capacity (about 3.5 l)

Fig. 83. Vital capacity of lungs (explanation in text).

The volume of air inspired and expired during ordinary respiration constitutes 500 ml. and is termed the *tidal* air.

In addition to the residual air the lungs usually also contain the so-called *supplemental* air which is exhaled in forced expiration. The volume of this air measures 1,500 to 1,800 ml.

In a usual inspiration we inhale less air than the lungs can hold after the maximum inspiration. The amount of air one can inhale in addition to the tidal air during maximum inspiration is known as the *complemental* air. Its volume, like that of the supplemental air, equals 1,500 to 1,800 ml.

The maximal volume of air that can be expired after maximal inspiration is referred to as the *vital capacity of the lungs* (Fig. 83). It includes the tidal (about 0.5 l), complemental (about 1.5 to 1.8 lit.) and supplemental air (about 1.5 to 1.8 lit.). The normal vital capacity for men constitutes approximately 3.5 to 4 litres, sometimes reaching 5 litres and more. For women the respective values are somewhat lower. The figure (in millimetres) obtained by multiplying the height (in centimetres) by 25 for men and by 20 for women is considered the normal vital capacity.

Athletes have a higher vital capacity; after the age of 40 it usually decreases.

The vital capacity of the lungs decreases when the pulmonary capillaries are filled with blood because at this time the volume of the alveoli is reduced. The vital capacity diminishes in decompensated diseases of the heart, this drop running in some measure parallel to that in the working capacity of the patient.

Role of the muscles of the bronchioles. The walls of the bronchioles contain smooth muscle fibres whose contractions constrict the bronchioles. The role of these muscles in normal respiration is not sufficiently understood as yet. The dilatation of some bronchioles with simultaneous constriction of others regulates the ventilation of different parts of the lungs.

The smooth muscles of the bronchioles are innervated by fibres of the vagus whose stimulation propagates impulses that cause the muscles to contract. An acute spasm of the bronchioles which leads to extreme difficulties in breathing (bronchial asthma) is due to a strong contraction of the smooth muscles of the bronchioles caused by impulses propagated along the fibres of the vagus. The impulses transmitted along the sympathetic fibres usually cause the bronchioles to relax. For this reason the substances that stimulate the sympathetic nervous system (adrenalin) and those that block the influence of the parasympathetic nervous system on the effectors (atropine) often relieve the spasm of the bronchioles, and the attack of bronchial asthma ceases.

Filling the lungs with air in initial respiration. During the foetal period the lungs contain no air and their collapsed alveoli are filled with a small amount of fluid. When the newborn comes into the world and no longer receives any oxygen from the mother's blood he makes the first inspiration; due to the contraction of skeletal muscles the thorax expands, the air enters the lungs and fills the distending alveoli. From that moment on the lungs distend with the expansion of the thorax during inspiration and diminish in volume during expiration. Atmospheric pressure forces the lungs against the inner walls of the thoracic cavity.

The so-called "hydrostatic test," used in medicolegal practice to determine whether the baby was born dead or alive, is based on the entrance of air into the lungs during the initial respiration. If the lungs were ever filled with air a certain amount of it remains in them and these lungs do not sink when placed in water. On the other hand, they sink if air had never entered them.

Weak respiratory movements occur even in the foetus and aspirate amniotic fluid into its lungs.

Inhaled, Exhaled and Alveolar Air. Dead Space

The composition of atmospheric air is extraordinarily constant; it contains 20.93 to 30.94 per cent oxygen, 0.03 to 0.04 per cent carbon dioxide and 79.02 to 79.04 per cent nitrogen and inert gases (including about 1 per cent argon and a negligible part of other gases). The air also always contains a certain amount of water vapour.

The expired air usually contains 15.5 to 18 per cent oxygen and 2.5 to 5 per cent carbon dioxide. The exhaled air is saturated with water vapour and has a temperature of 35 to 37°C.

If we collect the expired air in glass containers by successive portions of 50 ml., the air leaving the lungs in one expiration will take up 10 to 12 containers. An analysis of the air will show that the first 2 or 3 portions collected in the beginning of the expiration is of the same composition as that of the atmosphere. The subsequent portions contain increasingly more carbon dioxide and less oxygen, with the last 5 or 6 samples, i.e., the air leaving the lungs towards the end of expiration, having about 5.5 per cent carbon dioxide and about 14 per cent oxygen. The difference in the composition of the first and last portions of the exhaled air is explained by the fact that the *exhaled air contains not only alveolar air, i.e., the air which filled the alveoli and took part in the gaseous exchange with the blood, but also the air that filled the air passages (the oral and nasal cavities, the trachea and the bronchi).* No exchange of gases between the blood and the air takes place through the comparatively thick walls of the air passages which contain relatively few capillaries. Hence, the air in the air passages does not take part in the gaseous exchange and this space is called the dead space. The air found in it warms up and absorbs water vapour.

The dead space has a volume of approximately 150 ml. (120 to 180 ml.). There are indications that during increased pulmonary ventilation the volume of air that does not take part in the gaseous exchange somewhat increases. The volume of the air reaching the alveoli with each inspiration is smaller than that of the tidal air by the volume of the dead space. It follows that in rapid but shallow breathing the amount of air passing through the pulmonary alveoli (*alveolar ventilation*) is smaller than in slower but deep respiration. Rapid but shallow breathing may, therefore, supply the body with insufficient oxygen.

CHAPTER 21

RESPIRATORY FUNCTION OF THE BLOOD AND TISSUE RESPIRATION

The respiratory function of the blood consists in transporting oxygen from the alveolar air in the lungs to the tissues and carbon dioxide from the tissues to the alveolar air in the lungs.

Partial Pressure of Gases in Alveolar Air and Solubility of Gases in the Blood

The respiratory cycle begins with oxygen consumption and ends with the elimination of carbon dioxide. The gaseous exchange takes place between the blood and the alveolar air.

According to Dalton's Law the total pressure of a gas mixture equals the sum of the partial pressures of the gases composing it. The partial pressure of a gas in a mixture refers to the pressure the gas would exert if it alone occupied the volume of the whole mixture. If the total pressure of a gas mixture equals P mm. and the volume of the given gas corresponds to a the partial pressure of the gas p will be equal to $p = P\,\frac{a}{100}$.

The pressure of the alveolar air, if we disregard the very small variations at moments of inhalation and exhalation, equals atmospheric pressure (B).

Since the alveolar air is saturated with water vapour and the pressure of water vapour saturating the space it occupies at the temperature of the human body (37° C) corresponds to 47 mm. Hg the total pressure of the alveolar gases—N_2, O_2 and CO_2 is equal to *B*—47. With *B* equal to 760 mm. the total pressure of these gases will, consequently, be 713 mm. Hg. If the content of nitrogen equals 80.7 per cent the partial pressure of nitrogen (pN_2) will be 713 mm. $\times$ 0.807 = 575 mm.; the partial pressure of oxygen (pO_2), considering its content of 14 per cent, will be 713 mm. $\times$ 0.14 = = 100 mm., while the partial pressure of carbon dioxide (pCO_2) contained in the alveolar air in a concentration of, say, 5.5 per cent will be approximately 40 mm.

To determine the partial pressure (*p*) of each gas separately the composition of the alveolar air is analysed. To collect the alveolar air one end of a wide and long tube (1.5 to 2 m.) is taken in the mouth and a deep expiration is made. The air which fills the part of the tube closest to the mouth at the end of the expiration is the alveolar air that is collected in a container for analysis.

The amount of gas (in millilitres at a 760 mm. Hg pressure and 0° C temperature) dissolved in one ml. of liquid with its partial pressure corresponding to one atmosphere is designated as the *coefficient of solubility* of a given gas.

Table 5 gives figures of the solubility of gases.

Table 5

Coefficients of Gas Solubility at a Temperature of 38°

(After Van Slyke et al.)

Solvent	Coefficient of solubility		
	CO_2	O_2	N_2
Water	0.545	0.023	0.013
Blood plasma	0.510	0.021	0.012
Whole blood	0.470	0.023	0.013
Erythrocytes	0.440	0.026	0.015

If a gas is in contact with a liquid it dissolves in the liquid and after some time (the thinner the layer of liquid the sooner) a state of dynamic equilibrium is attained: the number of particles of gas that enter the liquid from the gas medium per unit of time equals the number of particles of gas that go back from the liquid to the gas medium. According to Henry's Law the concentration of gas in a solution which is in contact with the gaseous phase is proportional to the partial pressure of the gas over the solution. The greater the concentration of gas in the solution the more of its molecules escape the solution into the gaseous medium which does not contain the given gas (or into a vacuum). This tendency of the gas to pass from a liquid into a gaseous phase is called the *tension of gas* in a liquid. The molecules of the dissolved gas will escape into the space over the solution until the tension of the gas in the solution equals the partial pressure of this gas in a closed space over it (i.e., until the number of the molecules leaving the solution per unit of time equals the number of molecules entering the solution). It follows that the tension of a gas is measured by the partial pressure of this gas in equilibrium with the solution.

Thus, the measurement of the partial gas pressure, found in a state of dynamic equilibrium with a solution, makes it possible to determine the tension of the given gas in the liquid.

To determine the tension of a gas in a liquid we make use of *tonometers*. A tonometer is a glass vessel in which the liquid is in contact with a very small amount of air (in order that the exchange of gases between it and the liquid does not affect the tension of the gas in the latter). When an equilibrium between the gas dissolved in the liquid and the air over it is established the mixture of the gases of this air is analysed and the partial pressure of the gas in the bubble over the solution gives the tension of the gas in this solution.

With the coefficient of solubility of the gas and its tension in the liquid known it is easy to calculate the amount of the dissolved gas. For example, in 1 ml. of blood, which is in a state of equilibrium with the alveolar air at a temperature of 37° C, approximately the following amounts of gases will be dissolved.

CO_2	O_2	N_2
$\frac{0.47 \times 39}{760} = 0.0241$ (ml.)	$\frac{0.023 \times 98}{760} = 0.0029$ (ml.)	$\frac{0.013 \times 575}{760} = 0.0098$ (ml.)

The figures 39, 98 and 575 are the mean values of the partial pressure of the respective gases in the alveolar air (in mm. Hg).

Diffusion of Gases and Their Passage Through Alveolar Walls

The diffusion of gases from the alveolar air into the blood and back may be schematically regarded as occurring through a thin (approximately 4 μ thick) complex membrane which separates the alveolar air from the circulating blood. In accordance with the law of diffusion the amount of oxygen (O_2) diffusing into the blood through this membrane per unit of time, i.e., the total consumption of O_2 per minute, may be expressed by the following equation:

$$(O_2) = K\,(p_a - p_k),$$

where p_a is partial pressure of oxygen in the alveolar air, p_k is its tension in the blood and K is an individual constant value depending on the size of the total surface of the alveoli through which diffusion occurs and on the thickness and properties of the membrane which separates the blood from the alveolar air. If we express the pressure in mm. Hg, K becomes equal to O_2 when $p_a - p_k = 1$ mm. It follows that K is the total amount of oxygen which would diffuse from the alveolar air into the blood per minute if the difference between the partial pressure of oxygen in the alveolar air and the tension of oxygen in the blood flowing to the lungs were only 1 mm. Hg. This value of K is designated as the ***diffusion coefficient*** (it should not be confused with the coefficient of diffusion used in physical chemistry to designate the amount of substance diffused through a surface of 1 cm.^{2} per unit of time and with a concentration gradient equal to one).

The diffusion coefficient for oxygen varies considerably in different people and even in the same person under different conditions, usually constituting 25 to 65 ml. For CO_2 this coefficient is much higher because of the much greater solubility of CO_2 as compared with O_2.

All gases pass from regions of higher partial pressure to regions where their partial pressure (or tension) is lower.

The tension of carbon dioxide in the venous blood flowing to the lungs through the pulmonary artery in a healthy person at rest is usually 45 to

48 mm. Hg, whereas its partial pressure in the alveolar air is close to 40 mm. Hg. The tension of oxygen in the blood flowing to the lungs (at rest) is usually between 70 and 80 mm. Hg, while in the alveolar air its partial pressure ordinarily constitutes about 100 mm. Hg. Owing to this difference between the tensions in the blood and the partial pressures in the alveolar air (for CO_2 higher in the blood than in the alveolar air and for O_2 higher in the alveolar air than in the blood) carbon dioxide passes from the blood into the alveoli and the oxygen from the alveoli into the blood. It is obvious that as a result the tension of CO_2 in the blood circulating through the lungs drops, while that of oxygen rises. The tension of CO_2 in the *arterial* blood leaving the lungs is, therefore, lower and that of oxygen higher than in the venous blood flowing to the lungs.

The partial pressure of CO_2 in the alveolar air is very close to the pressure of CO_2 in the arterial blood, always being somewhat lower than the latter (approximately by 0.4 mm. Hg). The partial pressure of oxygen in the alveolar air is always somewhat higher (5 to 10 mm. Hg) than its tension in the arterial blood leaving the lungs.

Secretion of gases through alveolar walls. Numerous attempts have been made (Bohr, Haldane) to regard the passage of oxygen from the alveolar air into the blood not only as a result of the diffusion of gases but also as a result of secretory activity of the alveolar epithelium.

To prove the phenomenon of oxygen secretion in the lungs investigators tried to find a possibility for the passage of oxygen from regions of its lower tension to regions of its higher tension contrary to the laws of diffusion. However, no one has been able to demonstrate the possibility of such passage.

Secretion of oxygen has been authentically established in its passage from the blood to the swimming bladder in fish. It is well known that the partial pressure of oxygen in the swimming bladder of some fishes is higher than the tension of oxygen in their blood. If, however, the branches of the vagus innervating the bladder are cut the partial pressure of gases in the bladder becomes equal to the pressure of the gases in the blood flowing to it. Thus, the passage of oxygen from the blood into the cavity of the swimming bladder in fishes is a secretory process subject to nervous influences.

Though oxygen penetrates from the lungs into the blood by diffusion this process cannot be reduced to physical factors alone. The conditions of gas diffusion change with alterations in the physiological state of the body. Changes in the conditions of its activity may alter the flow of blood through the lungs, the repletion of the latter with blood, the permeability of the epithelium of the pulmonary alveoli and the endothelium of the pulmonary capillaries. Thus, at rest the lungs contain about 60 ml. of blood, while during hard work the blood content in the pulmonary vessels rises to 100 ml.

Changes in the filling of the lungs with blood and in the permeability of the membranes which separate the blood from the pulmonary air may depend on nervous influences exerted on the pulmonary vessels and tissues (the alveolar walls have endings of afferent and efferent nerve fibres). The possibility of a reflex origin of nervous influences which change the permeability of the alveolar membranes has been shown in experimental studies of pulmonary oedema. Injection of large amounts of a physiological solution into the blood of the rabbit does not of itself lead to oedema of the lungs. But if this action is combined with a stimulation of the interoceptors (by adding substances stimulating them, for example, nicotine, to the liquid perfused through the vessels of an intestinal loop which has retained only neural connections with the body) acute oedema of the lungs develops very rapidly (within 3 to 8 minutes) as a result (Kan, Chernigovsky). This phenomenon is, apparently, conditioned by reflex influences on the permeability of the capillaries and epithelium of the lungs.

Changes in the tension of the blood gases in inhaling gas mixtures rich in carbon dioxide or deficient in oxygen. If man inhales a mixture of carbon dioxide with oxygen or with air the escape of CO_2 from the blood into the lungs ceases when the partial pressure of carbon dioxide in the alveolar air equalizes the tension of CO_2 in the venous blood flowing to the lungs. But if as a result of inhaling a gas mixture abounding in CO_2 the partial pressure in the alveoli exceeds the tension of CO_2 in the blood the carbon dioxide will begin to pass from the alveolar air into the blood. In this case the escape of CO_2 from the blood will be resumed when the tension of CO_2 in the venous blood, into which carbon dioxide continuously passes from the tissues, rises above the artificially increased partial pressure of the carbon dioxide in the alveolar air. The passage of O_2 from the alveolar air into the blood also ceases in a similar manner.

If a gas mixture deficient in oxygen is inhaled the partial pressure of oxygen in the alveolar air drops below its tension in the venous blood flowing to the lungs.

The principle (proposed by Fick) for determining the tension of carbon dioxide in the venous blood flowing to the lungs from the right ventricle is based on the foregoing facts. The person studied inhales from a bag a mixture of air or oxygen with 4 to 5 per cent carbon dioxide, the expired air going back into the bag. Thus the partial pressure of CO_2 is artificially raised in the alveolar air. When the partial pressure of CO_2 in the alveolar air equalizes the tension of CO_2 in the mixed venous blood the carbon dioxide will cease passing from the blood into the alveoli (and will not pass from the alveoli into the blood). The equal content of CO_2 in the inspired and the alveolar air will indicate the cessation of carbon dioxide exchange between the alveolar air and the blood. The partial pressure of CO_2 in the air equals its tension in the mixed venous blood. With this we can calculate the percentage of the carbon dioxide content in the mixed venous blood of the given subject (see curve in Fig. 87).

It is difficult directly to determine the tension of oxygen in mixed venous blood; in experiments on animals this question is studied by making a puncture in the right cardiac ventricle. In man the tension of oxygen in the blood of the right ventricle is established by the data received in determining the minute volume of the heart (p. 203).

In certain cases (for example, to ascertain the diagnosis of congenital heart disease for the purpose of its subsequent surgical treatment) a rubber catheter with a tip opaque to X-rays is pushed under roentgenoscopic control through a cut in the human ulnar vein along the veins to the heart. Five to ten ml. of blood can thus be collected directly from the right heart in order to study the variations in pressure in the right heart and the pulmonary artery.

Exchange of Gases Between the Blood and the Tissues

The tissues continuously consume oxygen and produce carbon dioxide. Owing to this the tension of oxygen in the cells falls while the tension of carbon dioxide rises. As a result oxygen diffuses from the tissue fluid into the cells and CO_2 diffuses in the opposite direction. The oxygen impoverishment of the tissue fluid which contacts the walls of the capillaries leads to diffusion of oxygen from the blood into the tissue fluid and of carbon dioxide from the tissue fluid into the blood.

The higher the tissue metabolism, the lower the tension of oxygen in the tissues and, therefore, the greater the difference between the tension of oxygen in the tissues and in the blood. In the portions of the tissues the farthest removed from the capillaries the tension of oxygen drops almost to zero.

The importance of the dilatation of the capillaries, which are constricted at rest, for the supply of a hard working organ, for example, a muscle, is obvious.

Methods of Analysing Blood Gases

The first device which made it possible to obtain very precise information on the content of gases in the blood was the "absorption-meter" designed by I. Sechenov in 1858. The device was based on pumping the gases out of the blood into a vacuum over mercury. Repeated pumping into a continuously renewed vacuum makes it possible fully to extract all the gases of the blood—oxygen, carbon dioxide and nitrogen. The extracted mixture of gases is then subjected to a quantitative analysis.

The best modern instruments (for example, Van Slyke's apparatus) are built on the same principle. The improvements in the instrument consist in its smaller size, the ease of operation and in the fact that much less time is required for the analysis. Besides, in order more effectively to shift the carbon dioxide from the salts of carbonic acid to the blood, which is in the apparatus, organic acids are added, whereas to displace the oxygen a solution of potassium ferricyanide $[K_3Fe(CN)_6]$, which changes haemoglobin to methaemoglobin, is added.

To determine the amount of O_2 and CO_2 contained in the blood at different partial pressures of these gases the blood is mixed with a gas mixture of a definite composition. This is attained by shaking up a certain amount of blood in a closed glass vessel with a gas mixture of a precisely known composition and at a precisely known temperature, after which the content of the gases in the blood is determined.

A method has been developed which makes it possible to determine the oxygenation of the blood without resorting to chemical analysis; this method measures the content of oxyhaemoglobin in the blood by the latter's absorption of light rays (Millikan, Kraner and Kreps). The method is based on the fact that in the red part of the spectrum (wavelength 620 to 680 mμ) the absorption of light by haemoglobin is several times as high as its absorption by oxyhaemoglobin. A change in the oxygenation of haemoglobin, therefore, sharply affects the absorption of light in this part of the spectrum. On the contrary, in the green part of the spectrum there are sections where both pigments absorb light equally and the degree of light absorption, therefore, depends on the total amount of pigment. Comparing the measurements of the absorption of light in two different parts of the spectrum makes it possible to determine the degree of oxygenation of the blood. For this purpose a beam of light passing through a layer of blood is trained on the light-sensitive layers of two photo-cells of an oximeter; one of these cells is covered with a red light filter and the other with a green light filter. The greater the oxygenation of the blood the more red light passes through the blood and the more electric current there is in the photo-cell covered with the red filter. The currents from the photo-cells are boosted by means of a system of cathode valves and their intensity is read on the scale of a galvanometer calibrated during preliminary determination of current intensity at different oxyhaemoglobin levels of the blood.

By means of the oximeter it is possible quickly to determine not only the oxygenation of blood *in vitro*, but also the oxygenation of the blood flowing through the vessels of the lobe of the human ear. If the ear is warmed (for which purpose the rays of the lamp, which serves as the source of light in the oximeter, are used) the capillaries of the ear dilate to such an extent that the blood flowing through the ear becomes very similar to arterial blood in oxygen content. By passing light through the warmed lobe of the ear to a photo-cell fastened on the ear it is possible to register the oxyhaemoglobin content (in percentages to the total haemoglobin content, which determines the oxygen capacity) in the arterial blood of man and to establish in the well and in the sick the changes in the oxygenation of the blood under different conditions (for example, in hypoxia, etc.).

Transport of Oxygen in the Blood

Oxygen capacity of the blood and of the haemoglobin. The amount of oxygen physically dissolved in the blood is insignificant. With the usual partial pressure values of oxygen in the alveolar air at a temperature of 37°C only about 0.3 ml. of oxygen dissolves in 100 ml. of blood plasma, while the whole arterial blood normally contains 18 to 21 per cent of oxygen. It follows that nearly all of the oxygen in the arterial blood is chemically combined with the haemoglobin rather than dissolved. The *oxygen capacity of the blood, i.e., the total amount of oxygen contained in the blood when it is fully oxygenated,* is, therefore, practically determined by the amount of oxygen with which haemoglobin can combine. *Each gram of haemoglobin can combine with 1.34 ml. of oxygen, thus forming oxyhaemoglobin.*

One gram-molecule of haemoglobin ($M = 67{,}000$) combines with 4 gram-molecules of oxygen, i.e., $4 \times 22{,}400 = 89{,}600$. Consequently, there is $89{,}600 : 67{,}000 = 1.34$ ml. of oxygen per one gr. of haemoglobin. We obtain the same value if we proceed from the fact that one gram-atom (56 gr.) of iron combines with one gram-molecule of oxygen (22,412 ml.) and 100 grams of haemoglobin contain 0.335 gr. of iron. Experience confirms the correctness of this computation.

Since the blood of healthy people contains 14 to 16 gr. of haemoglobin per 100 ml. of blood the oxygen capacity of their blood corresponds to 18 to 21 per cent.

Saturation of haemoglobin with oxygen under varying tensions. The reaction between haemoglobin and oxygen is reversible. It may be schematically expressed by the following equation:

$$\underset{\text{haemo-globin}}{Hb} + \underset{\text{oxy-gen}}{O_2} \rightleftarrows \underset{\text{oxyhaemo-globin}}{HbO_2}$$

With a rise in tension, i.e., with an increased concentration of dissolved oxygen in the blood, the equilibrium shifts towards an increase in the oxyhaemoglobin content. With a decrease in the oxygen tension the equilibrium shifts in the opposite direction, i.e., oxygen dissociates from oxyhaemoglobin. With oxygen tension dropping to zero oxygen entirely dissociates from oxyhaemoglobin and the blood contains only haemoglobin.

The interdependence between the oxygen tension (pO_2) and the amount of oxyhaemoglobin may be expressed graphically. For this purpose the oxygen tension in millimetres of mercury is marked along the abscissa and the oxyhaemoglobin in percentages of its amount formed during *full* oxygenation of the haemoglobin is marked along the ordinates. The interdependence between these values is expressed by a curve called the curve of haemoglobin oxygenation or the *curve of oxygen dissociation* (Fig. 84).

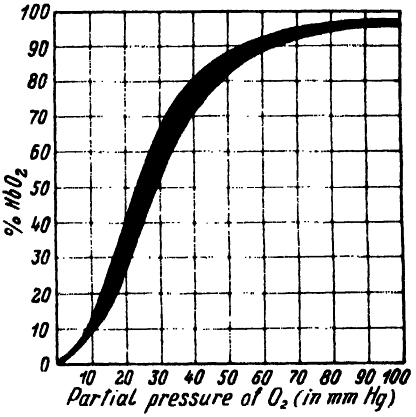

Fig. 84. Oxygen dissociation curve.
Heavy line shows limits in curve variations healthy people (after Barcroft).

To plot this curve several samples of the same blood are saturated with gas mixtures having different, but precisely known, partial pressures of oxygen. The total oxygen content in the blood is then determined by the previously-described method. A correction for the amount of plasma dissolved oxygen is then made, expressing its content in percentages to the amount of oxygen combined with haemoglobin. The part of haemoglobin, transformed to oxyhaemoglobin is then determined. By marking the values of pO_2 along the abscissae and the percentages of the oxyhaemoglobin content along the ordinates a series of points is obtained. By joining these points we obtain the *oxygen dissociation curve.*

Curve of oxygen dissociation. The curve of oxygen dissociation (Fig. 84), studied in detail by N. Bohr, D. Barcroft, J. Haldane and other investigators, begins at the point of intersection of the axes of the coordinates. This corresponds to the fact that at zero tension of oxygen there is no oxyhaemoglobin in the blood. With a rise in the tension of oxygen the curve of oxyhaemoglobin goes up gently at first and then rises more sharply. Thus, with an oxygen tension of 10 mm. Hg the human blood contains 10 to 15 per cent oxyhaemoglobin; with a tension of 20 mm. Hg it contains 30 to 35 per cent and with a pO_2 of 30 mm. Hg the oxyhaemoglobin content reaches 50 to 60 per cent. With a further increase in the oxygen tension in the blood the curve of oxygen dissociation flattens out again; with a pO_2 of 40 mm. the content of oxyhaemoglobin is 70 to 75 per cent; with a pO_2 of 50 mm. it corresponds to 80 or 85 per cent; with a pO_2 of 60 mm. it reaches approximately 90 per cent. After that the curve runs nearly horizontally; an increase in the pO_2 from 60 to 80 mm. adds 6 per cent oxyhaemoglobin and from 80 to 100 mm. only 2 per cent. The curve thus asymptotically approaches a horizontal line which signifies the limit (i.e., 100 per cent) of saturation.

As a whole the curve is S-shaped; at first it rises sharply and then more gently.

This complex nature of the haemoglobin-oxygenation curve is due to the fact that there are four haemin groups in the haemoglobin molecule and the reversible reaction between haemoglobin and oxygen is not a one-stepped reaction as was schematically presented above.

The sharp rise of the curve of oxygen dissociation in the region of 20 to 40 mm. Hg oxygen pressures is of considerable physiological importance chiefly under conditions of oxygen hunger (for example, in a rarefied atmosphere). Owing to this the blood may give off considerable amounts of oxygen to the tissues without letting the partial pressure of oxygen, which governs the rate of its diffusion into the tissues, drop below 20 to 30 mm.

The approach of the curve of oxygen dissociation to a horizontal line at an oxygen pressure of over 80 mm. Hg indicates that a drop in the partial pressure of oxygen in the lungs from 100 to 80 mm. hardly affects the oxygenation of haemoglobin. An ascent from a plain to an altitude of up to 2,000 metres does not, therefore, appreciably decrease the oxygenation of the arterial blood.

Factors affecting the curve of oxygen dissociation. The general nature of the curve of oxygen dissociation is the same for various classes of animals. It begins at the point of intersection of the coordinates in all cases; at an oxygen tension above 100 mm. Hg practically all of the haemoglobin (96 to 98 per cent) always changes to oxyhaemoglobin; the curve is S-shaped in every case. However, the curve may not always rise so sharply. In connection with this the curve in the diagram shifts either to the left (when rising sharply) or to the right (when rising more gently).

In some deep-sea fishes who live in water containing extremely little oxygen the haemoglobin is almost fully transformed into oxyhaemoglobin at a tension of oxygen which does not exceed 10 mm. Hg.

During the foetal period the haemoglobin has a greater affinity for oxygen than the haemoglobin contained in the blood of adult species. This facilitates passage of oxygen from the blood of the mother into that of the foetus (A. Ginetsinsky). The foetal form of haemoglobin is replaced by the adult type during the first days of life.

A rise in temperature considerably accelerates oxygen dissociation, but hardly affects the rate at which haemoglobin combines with oxygen. This causes the curve of oxygen dissociation to flatten towards the right during a rise in temperature.

The curve of oxygen dissociation is also modified by changes in the hydrogen ion concentration of the blood. A shift in the blood reaction in the direction of alkalinity makes the oxygen combine more intensively with haemoglobin and, consequently, displaces the curve to the left. Contrariwise, a shift of the reaction towards acidity promotes greater oxygen dissociation and the curve shifts to the right.

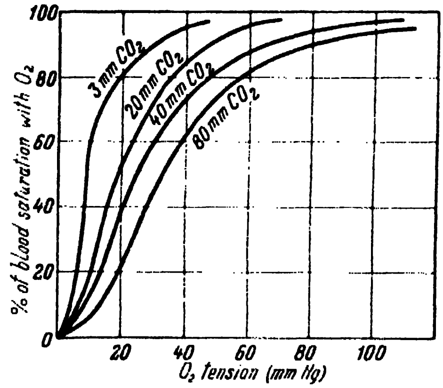

Fig. 85. Influence of CO_2 tension on oxygen dissociation curve (after Haldane)

Changes in the content of free carbonic acid in the blood are the most important reason for the variations in its reaction: the higher the tension of CO_2 the more is the curve of dissociation displaced to the right (Fig. 85). Interacting with haemoglobin CO_2 affects the curve of oxygen dissociation more than it would be affected by an accumulation of carbonic acid which would shift the reaction of the blood towards acidity (S. Severin et al.).

The influence of CO_2 is particularly pronounced in the steeply climbing part of the curve of oxygen dissociation, i.e., at oxygen tensions of up to 50 mm. Hg. For this reason the passage of CO_2 into the blood aids in splitting the oxygen from the haemoglobin in the tissues where the tension of the oxygen in the blood of the capillaries drops. But at oxygen tensions of 80 to 100 mm. mercury and higher the haemoglobin is almost fully saturated with oxygen at both high and low tensions of CO_2.

Transport of oxygen by the blood from the lungs to the tissues. At the barometric pressure of over 600 mm. Hg (i.e., at altitudes of up to 2,000 metres above sea level) the arterial blood of healthy people is 95 to 98 per cent oxygenated, and contains $1.34 \times X$ ml. O_2, where X is the amount of haemoglobin per 100 ml. of blood.

In the blood of the capillaries of the systemic circulation the tension of oxygen falls because the oxygen dissolved in the plasma passes through the walls of the capillaries into the tissues where the tension of O_2 is the lower the more oxygen is consumed by the tissue oxidative processes. The former equilibrium between the dissolved oxygen and the oxyhaemoglobin is disturbed and the oxyhaemoglobin begins to break up into haemoglobin and oxygen. This process occurs all along the capillaries.

After the passage of the blood through the capillaries the tension of oxygen in the blood corresponds to about one-third of the sum of oxygen tensions in the arterial and venous blood constituting an average of 40 mm. Hg.

The curve of oxygen dissociation shows that the oxygen tension of 40 mm. Hg corresponds to a content of 70 to 75 per cent oxyhaemoglobin in the blood which is the average oxyhaemoglobin content in venous blood.

It should be borne in mind, however, that the content of oxygen in the venous blood at a certain oxygen tension must not be calculated by the curve of oxygen dissociation which has been determined for the arterial blood. Venous blood contains more CO_2, the reaction of the blood is slightly shifted towards acidity and, finally, the temperature of the blood (in the internal organs and muscles) is also somewhat higher than in the arteries. All these factors cause a shift of the curve of oxygen dissociation to the right, i.e., they promote greater oxygen dissociation and greater liberation of oxygen to the tissues.

The oxygen content in mixed venous blood, i.e., in the blood of the right heart, can be easily computed if we know the minute volume of the heart.

If the blood pumped by the right ventricle takes up in the lungs n ml. of oxygen per minute (the value of the total consumption of oxygen by man per minute) with the minute volume of the heart corresponding to M ml. of blood, then every 100 ml. of blood take up in the alveolar air the following amount of oxygen (X):

$$X=\frac{n\times 100}{M}\ \text{ml.}$$

If we designate the content of oxygen in the arterial blood as A, the content of O_2 in the venous blood flowing to the lungs from the right heart may be expressed in the following formula:

$$A-\frac{n\times 100}{M}\ \text{ml.}$$

Thus, with the minute volume of 4,000 ml., a 240 ml. oxygen consumption per minute and 20 volume per cent oxygen in the arterial blood its content in venous blood will constitute:

$$20-\frac{240\times 100}{4{,}000}=20-6=14\ \text{ml.}$$

At muscular rest the oxygen content of venous blood flowing to the lungs constitutes approximately 65 to 75 per cent of the oxygen content of arterial blood, i.e., it corresponds to 12 or 15 ml. per 100 ml. of blood. Thus, the difference between the oxygen content in the blood flowing from the lungs (arterial) and that flowing to the lungs (mixed venous), the so-called arteriovenous difference, usually constitutes 4.5 to 5.5 ml. of oxygen per 100 ml. of blood. In hard muscular work the arteriovenous difference in oxygen content may considerably increase (Fig. 86).

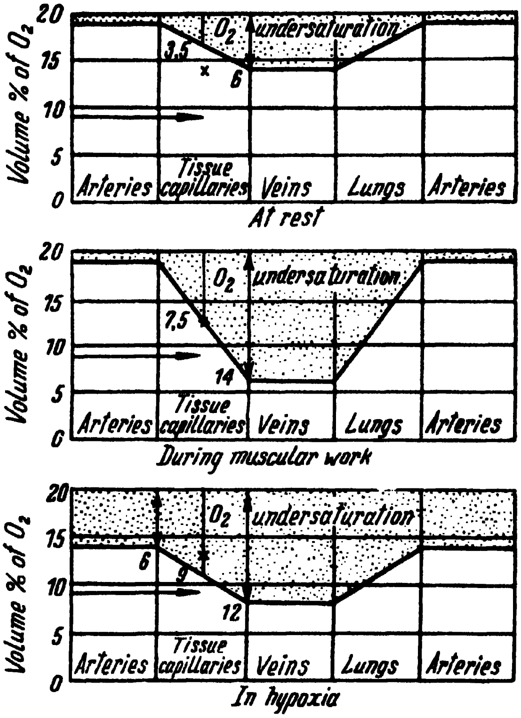

Fig. 86. Oxygen content of venous blood flowing to heart: top—at rest, centre—during sharp increase of oxygen loss in muscles as result of muscular work, and bottom—in underoxygenated blood due to respiratory hypoxia (after A. Charny).

The oxygen content of venous blood leaving various organs is the lower, the higher the metabolism in these organs and the less blood flows through them per unit of time.

With the transformation of oxyhaemoglobin into haemoglobin the colour of the blood changes: from scarlet it becomes dark-lilac. The less oxyhaemoglobin in the blood and the more reduced haemoglobin, the darker the blood. When the content of reduced haemoglobin in the venous and capillary blood exceeds 5 to 6 gr. per 100 ml. of blood the skin and the mucous membranes acquire a greyish-blue colouring. This phenomenon is called *cyanosis*.

Content of carbon dioxide, free carbonic acid and bicarbonates in the blood. *The content of carbon dioxide in the blood is directly proportional to its tension and is designated as pCO_2 (Fig. 87). The coefficient of carbon* dioxide solubility in the blood at a temperature of 38° C is 0.47. Thus, with a pCO_2 of 40 mm. Hg the amount of dissolved carbon dioxide in arterial blood will be 2.4 ml. per 100 ml. of blood (p. 196). In venous blood the partial pressure of carbon dioxide increases by 7 to 10 mm. Hg which leads to an increase in the amount of carbon dioxide dissolved in the blood by 0.5 ml. per 100 ml. of blood. Carbon dioxide enters into a reversible reaction with water and carbonic acid is produced:

$$CO_2 + H_2O \rightleftarrows H_2CO_3.$$

Because of the instability of H_2CO_3 the equilibrium is sharply displaced to the left so that there is approximately only one molecule of H_2CO_3 to 1,000 molecules of CO_2.

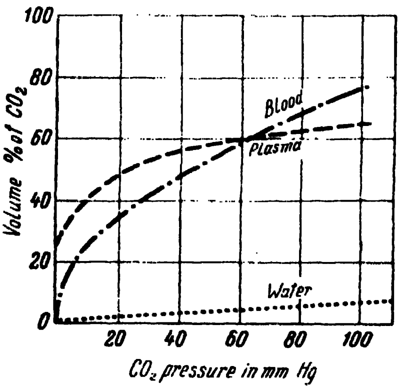

Fig. 87. Carbon dioxide content in plasma and in blood under different partial CO_2 pressures.

Lower line (dotted) shows amount of CO_2 dissolved in water.

Carbonic acid (H_2CO_3) is a weak acid capable of dissociating into $H^{\cdot}$ and HCO_3'' ions. The coefficient of its dissociation corresponds to $10^{-3.4}$. Since the amount of the H-ions produced must be compared to the sum of the concentrations of CO_2 and H_2CO_3 use is made of the apparent constant for this sum ($10^{-6.3}$ for water and $10^{-6.}$ for blood plasma) which is approximately 1/1000 of the true coefficient.

The content of free carbonic acid in the blood is so low that it is disregarded when the total amount of carbon dioxide in the blood is calculated. It is through carbonic acid, however, that its interaction with the various buffer systems of the blood is effected with the production or disappearance of the *bicarbonate form of carbonic acid.* It is impossible to understand the mechanism of CO_2 transport in the blood without considering the significance of this form. For example, a reaction with a bivalent anion of phosphoric acid proceeds as follows:

$$\underset{\substack{\text{carbonic}\\\text{acid}}}{H_2CO_3} + \underset{\substack{\text{bivalent}\\\text{anion of}\\\text{phosphoric}\\\text{acid}}}{HPO_4''} \rightleftarrows \underset{\substack{\text{anion of}\\\text{carbonic}\\\text{acid}}}{HCO_3'} + \underset{\substack{\text{univalent}\\\text{anion of}\\\text{phosphoric}\\\text{acid}}}{H_2PO_4}$$

The interaction of carbonic acid with other buffer systems, particularly its most important reaction with haemoglobin and the plasma proteins, proceeds according to the same pattern.

Each time the carbon dioxide content in the blood increases the amount of H_2CO_3 in it also increases, and a rise in the concentration of H_2CO_3 in a buffered fluid, such as the blood, inevitably leads to production of more bicarbonate. Contrariwise, any decrease in the content of carbon dioxide leads to a shift of the equilibrium in the above-mentioned reaction in the opposite direction.

The total amount of bicarbonates in the blood is much larger than the quantity of CO_2. According to the equation of buffer solutions (p. 52), with a 7.4 pH of the plasma the molecular concentration of bicarbonates is nearly 20 times as high as that of CO_2. The erythrocytes contain somewhat less pH than the plasma (7.1 to 7.15); here the concentration of bicarbonates exceeds that of CO_2 a little more than tenfold. The plasma contains mainly the bicarbonate of sodium ($NaHCO_3$); in the erythrocytes the bicarbonate of potassium ($KHCO_3$) prevails.

In arterial blood the carbon dioxide content of bicarbonates constitutes approximately 45 ml. per 100 ml. of blood (45 per cent by volume). In flowing through the capillaries the blood acquires carbon dioxide and carbonic acid owing to which the amount of bicarbonates also increases, the increase corresponding to that of the total amount of CO_2 in the blood by approximately 3.5 to 5 per cent by volume.

Carboanhydrase of the blood and its role. As before stated the formation of bicarbonates from CO_2 and their decomposition with formation of CO_2 is achieved through an intermediately formed substance—H_2CO_3.

The hydration of CO_2 and dehydration of H_2CO_3 proceed slowly compared with the other reactions of the respiratory cycle. On the other hand, the blood flows through the entire length of the capillary system, both in the tissues and in the lungs, in approximately one second.

If CO_2 hydration and H_2CO_3 dehydration in the blood occurred as slowly as they do in the inorganic systems the amount of metabolized carbon dioxide could not be eliminated from the body. As a matter of fact these reactions take place in the blood fast enough for redistribution of carbon dioxide between the blood, on the one hand, and the alveolar air or the tissues, on the other, to take place in one second. This is due to the fact that the rate of CO_2 hydration and H_2CO_3 dehydration in the blood increases because of a special enzyme in the erythrocytes known as *carbon anhydrase* or *carboanhydrase* (Roughton).

The carboanhydrase is a zinc-containing protein. Its action is depressed by sulfanilamides. Carboanhydrase accelerates the reaction of dissociation of H_2CO_3 ($H_2CO_3 \rightleftarrows CO_2 + H_2O$) and the reverse reaction of CO_2 hydration ($CO_2 + H_2O \rightleftarrows H_2CO_3$). The direction of the process depends on the concentration of the participating components. The content of carboanhydrase in the blood of various animals differs. Some poikilotherms have no carboanhydrase.

Since carboanhydrase is found in erythrocytes and the blood plasma contains none, the production and dissociation of H_2CO_3 take place mainly in the erythrocytes; the equilibrium in the distribution of CO_2 and HCO_3' between the plasma and the erythrocytes is disturbed and these substances pass from the erythrocytes into the plasma or back depending on the direction in which the equilibrium has shifted. As the blood flows through the capillaries of the systemic circulation, CO_2 diffuses into the blood plasma and then into the erythrocytes. With the participation of carboanhydrase CO_2 is transformed in the erythrocytes into H_2CO_3. H_2CO_3 partly interacts with the buffer systems of the erythrocytes and partly passes back into the plasma where it interacts with the buffers of the latter. Thus, the equilibrium between the various forms of carbon dioxide in the plasma is achieved by their exchange between the plasma and the erythrocytes.

Carbamino compounds of CO_2 in the blood. As early as the seventies of last century I. Sechenov discovered that haemoglobin could form unstable compounds with carbon dioxide. Sechenov's discovery was later contested by some investigators who reduced the role of haemoglobin in binding CO_2 entirely to the buffer mechanism. But towards the end of the twenties of our century the formation of an easily dissociating compound of haemoglobin and carbon dioxide (*carbaminohaemoglobin*) was firmly established.

Chemically this reaction consists in the interaction of amino-groups of haemoglobin with carbon dioxide:

$$R-NH_2+CO_2 \rightleftarrows R-NHCOOH.$$

This reaction is reversible with the state of equilibrium reached practically instantly.

The product of this reaction is a derivative of carbamic acid (NH_2COOH) which forms the moment particles containing an amino-group come in contact with carbon dioxide. This is why the carbon dioxide forming part of such compounds is designated as the carbamino compound of CO_2.

The reaction with carbon dioxide proceeds only in the presence of free amino-groups ($-NH_2$); the amino-groups which have added a proton ($-NH_3^{\cdot}$) do not interact with carbon dioxide. For this reason with a decrease in pH the amount of the carbamino compounds of CO_2 also decreases.

The total amount of the carbamino compounds of CO_2 in arterial blood is not large; it binds approximately 3 ml. of CO_2 per 100 ml. of blood. But when the blood passes through the capillaries the tension of CO_2 rises, part of oxyhaemoglobin is reduced to haemoglobin, the pH in the erythrocytes somewhat decreases and the content of the carbamino compounds of CO_2 increases, i.e., the amino-groups bind an additional amount of CO_2 (approximately 0.8 ml.). About 20 per cent of all the carbon dioxide entering the blood from the tissues (about 4 ml. per 100 ml. of blood) is, thus, transported from the tissues to the lungs as carbamino compounds of CO_2. In the lungs the partial pressure of CO_2 drops and, by virtue of the reversibility of the reaction, the CO_2 in carbamino compounds is almost instantly liberated.

Effect of oxygenation of the blood on its carbonic acid content. The partial pressure of CO_2 is an important factor affecting the total content of CO_2 in the blood. The higher it is the greater will be the amount of dissolved carbon dioxide, bicarbonates and the carbamino compounds of CO_2 in the blood.

The interdependence between the tension and total amount of CO_2 is shown in Fig. 87 in the form of a curve of blood saturation with CO_2.

In 1892 B. Verigo, one of I. Sechenov's pupils, ventilated separately one lung with hydrogen and the other with oxygen by means of a pulmonary catheter (thin tube inserted in a bronchus). The analysis of the air, collected separately from both lungs, showed that the lung through which oxygen had been passed liberated more CO_2 than the one where the blood could not be oxygenated. Twenty-two years later Haldane and his associates discovered that the blood saturated in tonometers with carbon dioxide could bind the more carbon dioxide the less oxyhaemoglobin and, consequently, the more reduced haemoglobin it contained (Fig. 88).

This phenomenon is conditioned by differences in the physicochemical properties of haemoglobin and oxyhaemoglobin. Both proteins are weak acids, but oxyhaemoglobin is the stronger acid of the two. The formation of oxyhaemoglobin must, therefore, be accompanied by a surrender of the hydrogen ion to the anions of the weak acids, in particular, to the bicarbonate ions. The total amount of anions and, consequently, the corresponding cations of potassium in the erythrocytes remain unchanged. By conventionally designating oxyhaemoglobin as $HHbO_2$, we can express this reaction by the following equation:

$$HHbO_2 + HCO_3' \rightleftarrows HbO_2' + H_2O + CO_2.$$

Besides, it has been shown that in the carbamino compounds oxyhaemoglobin also binds less CO_2 than does reduced haemoglobin. Both these factors tend to decrease the binding of CO_2 by the arterialized blood* as compared with the venous blood (Fig. 88).

The foregoing phenomenon is of great physiological importance to the transport of carbon dioxide by the blood. When the blood enters the capillaries of the tissues part of the oxyhaemoglobin loses its oxygen and changes to haemoglobin which is a weaker acid. In this case the blood acquires the capacity of additionally binding a certain amount of CO_2 without involving the usual buffer systems and, consequently, without a shift in the reaction. Owing to this the passage of CO_2 from the tissues into the blood causes a very insignificant change in the reaction of the blood (decrease in pH by only 0.03). The more vigorous the oxidative processes the more CO_2 forms in the blood and, at the same time, the higher the consumption of oxygen by the tissues and the corresponding oxygen impoverishment of the blood. Hence, the possibility for binding a larger amount of CO_2 by a volume unit of blood flowing through the tissues is to a certain extent ensured by a decrease in the content of its oxyhaemoglobin.

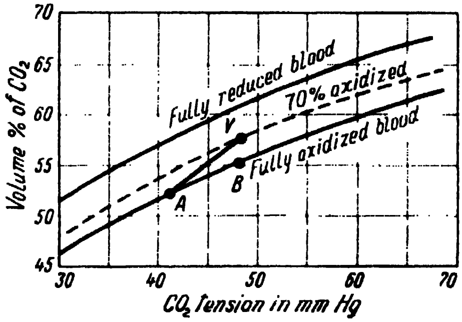

Fig. 88. Effect of oxygenation of blood on curve of CO_2 uptake by blood (explanation in text).

Fig. 88 shows the curves of binding carbonic acid by reduced blood (in which there is no oxyhaemoglobin) and by fully oxidized blood (in which there is only oxyhaemoglobin). These curves demonstrate that, for example, at a CO_2 tension of 55 mm. Hg the reduced blood contains 64 per cent CO_2, while the oxidized blood contains only 58 per cent, i.e., 6 per cent less. This is due, as has been said, to the fact that in the oxidized blood much more $K^{\cdot}$ is retained in the $KHbO_2$, while in the reduced blood $K^{\cdot}$ may be used for binding HCO_3'.

In the body the blood flowing through the capillaries is never fully reduced, and the dotted line in Fig. 88 shows the curve of carbon dioxide uptake by venous blood still oxygenated to 70 per cent of its oxygen capacity. Let us assume that in the arterial blood the tension of dissolved carbon dioxide is 42 mm. and in the venous blood

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* Oxygenated venous blood is called arterialized blood.

48 mm. Hg. If in passing through the capillaries the blood did not liberate oxygen the content of the combined carbon dioxide in the blood would increase, as is shown in Fig. 88, from point *A* to point *B*, i.e., it would rise from 52 to only 55 per cent. But since 30 per cent of oxyhaemoglobin in the capillaries changes to haemoglobin the process will be indicated by line *AV* rather than *AB*. This line joins the point which shows the content of carbon dioxide in the arterial blood at a CO_2 tension of 42 mm. Hg with the point on the dotted line which corresponds to a carbon dioxide tension of 48 mm. Hg. The position of point *V* shows that the venous blood still containing 70 per cent oxyhaemoglobin with a carbon dioxide tension of 48 mm. Hg contains not 55 per cent carbonic acid, as does the arterial blood, but 57 per cent.

In the lungs the above-mentioned phenomena proceed in the opposite direction in relation to CO_2 combination in the tissues. The oxygenation of haemoglobin produces oxyhaemoglobin which is more acid than haemoglobin. Owing to this a certain amount of potassium in the erythrocytes, used for combining with CO_2 to form bicarbonate in the reaction of H_2CO_3 with the reduced haemoglobin, recombines with the oxyhaemoglobin formed in the lungs from haemoglobin. This leads to the transformation of some bicarbonates into carbonic acid which with the aid of carboanhydrase dissociates into H_2O and CO_2. The amount of bicarbonates in the erythrocytes diminishes.

The H_2CO_3 formed with the aid of the carboanhydrase of the erythrocytes breaks up into CO_2 and H_2O. The total molecular concentration of the substances dissolved in the erythrocytes slightly diminishes and owing to a disturbance in the osmotic equilibrium between the erythrocytes and the plasma, water passes into the plasma and the volume of erythrocytes decreases.

Exchange of ions between the plasma and the erythrocytes. During respiration the blood plasma and the erythrocytes continuously exchange certain substances.

The membrane of erythrocytes is easily permeable to water, to certain anions (OH', Cl', HCO_3', the anions of lactic acid and some others) and to hydrogen ions (cations).

As the blood flows through the capillaries CO_2 passes from the tissues into the blood. Penetrating into the erythrocytes CO_2 is changed by carboanhydrase to H_2CO_3 which interacts with the buffer substances of the erythrocytes and is transformed into HCO_3' ions. The rise in the concentration of the latter forces a certain amount of them to leave the erythrocytes for the plasma in exchange for Cl' ions which pass from the plasma back into the erythrocytes. Owing to this exchange the concentration of bicarbonates increases in the erythrocytes and in the plasma, while the concentration of chlorides slightly rises in the erythrocytes and falls in the plasma.

An increase in the concentration of hydrogen ions in the plasma because of CO_2 entering the latter exerts a similar influence. The equilibrium between the plasma and the erythrocytes is disturbed and hydrogen ions penetrate from the plasma into the erythrocytes. But this passage is possible only when the hydrogen ions are accompanied by some anions, otherwise this would disturb the electric neutrality. The most concentrated anions in the plasma are those of chlorine and that is why they are the most frequent partners of hydrogen ions when the latter pass from the plasma into the erythrocytes.

As soon as the hydrogen ions penetrate into the erythrocytes they combine with buffer substances—phosphoorganic compounds—and, especially, with the haemoglobin anions. Because of this the total number of negative charges remains unchanged despite the penetration of the $H^{\cdot}$ and Cl' ions:

$$Hb' + (H^{\cdot} + Cl') \rightarrow HHb + Cl'.$$

Naturally, the total number of cations does not change either. But the total molecular concentration increases because of the rise in the concentration of the chlorine ions. Owing to this the osmotic pressure within the erythrocytes rises and causes a certain amount of water to pass from the plasma into the erythrocytes. The volume of erythrocytes slightly increases. In the lungs these phenomena occur in the reverse order.

Owing to the exchange of ions between the plasma and the erythrocytes the bicarbonate content in the plasma increases more with the saturation of the whole blood with carbon dioxide than with the saturation of the erythrocyte-free plasma. In the first case, due to the high buffering capacity of the erythrocytes, with the increase of carbonic acid in the plasma a considerable amount of hydrogen ions passes from the plasma into the erythrocytes and is accompanied by chlorine ions. The chlorine anions are replaced by anions of carbonic acid. The distribution of cations remains the same.

Thus, to determine the amount of bicarbonates in the plasma in estimating the pCO_2 the whole blood must first be saturated with carbon dioxide and the plasma separated by centrifuging (the plasma thus obtained is known as the *true* plasma). If the plasma is separated at a low CO_2 tension and is then saturated with carbon dioxide in the absence of erythrocytes the bicarbonate content in it will be lower (*separated* plasma).

Summary Changes in the Blood During the Respiratory Cycle

In the lungs the venous blood is oxygenated. The oxygen tension rises and the amount of oxyhaemoglobin increases. Contrariwise, the tension and content of CO_2 in the blood diminish owing to the passage of CO_2 from the blood into the pulmonary alveoli. Though the liberation of carbon dioxide from the blood into the lungs is partly compensated by the production of oxyhaemoglobin, which is a stronger acid than haemoglobin, the reaction of the blood still shifts slightly towards alkalinity and its pH turns out to be higher than in the venous blood. In connection with the more pronounced alkalization of the plasma and the higher capacity of the erythrocyte buffer substances the hydrogen and chlorine ions pass from the erythrocytes into the plasma accompanied by water. The volume of the erythrocytes slightly diminishes.

As the arterial blood flows through the tissue capillaries all the above-described processes run in the reverse order. With the return of the blood to the lungs the entire cycle of changes is repeated.

Table 6 characterizes the quantitative aspect of the aforementioned changes.

Table 6

Changes in the Properties of the Blood During the Respiratory Cycle
(mean figures)

	Arterial	Venous
O_2 tension (in mm. Hg)	98	40
Oxygen content (in volume %)	19	14.5
CO_2 tension (in mm. Hg)	39	46
Total CO_2 content (in volume %)	48	52
pH of plasma	7.38	7.35
pH of erythrocytes	7.12	7.11
Volume of erythrocytes (in % to the volume of the blood)	40	40.4

CHAPTER 22

REGULATION OF RESPIRATION

Respiratory Centre

In the beginning of the 19th century it was discovered (Legallois, Flourens) that all vertebrates retained their respiratory movements after removal of the cerebrum above the medulla oblongata, but that these movements inevitably and immediately ceased after destruction of the medulla or after cutting the spinal cord below the medulla. Inhibition of the functions of the medulla by cooling (without destroying it) also results in cessation of breathing.

In cooling the medulla oblongata or after cutting the spinal cord below the medulla the neurons, whose axons directly innervate the respiratory muscles, are not affected because their cell bodies are located in the cervical and thoracic segments of the spinal cord. However, after severance from the medulla these spinal neurons become inactive. This is clearly seen in animals whose spinal cord is cut between the lower cervical and the upper thoracic segments. In this case the neurons, which innervate the diaphragm, retain contact with the medulla because their cell bodies lie in the third to fifth cervical segments of the spinal cord. The cell bodies of the neurons innervating the intercostal muscles are located in the thoracic segments of the spinal cord and when the latter is cut in its lower cervical division they are disconnected from the medulla. That is why the rhythmic respiratory movements of the diaphragm are retained, while the respiratory movements of the ribs cease when the spinal cord is thus cut.

N. Mislavsky

It follows that the rhythmic respiratory movements are performed only when the motoneurons of the spinal cord are connected with the medulla. The latter contains the nervous structures necessary for the performance of the respiratory movements. These structures are known as the respiratory centre.

In the first half of the 19th century the respiratory centre was conceived as the "vital knot" (Flourens) which occupies a very small space in the floor of the fourth ventricle. The studies of the respiratory centre were the point of departure for the development of the entire teaching of the localization of functions, the teaching which not infrequently assumed a metaphysical character: the central nervous system was divided into innumerable "centres" with different functions, each of which presumably always played the same part determined by the properties and structure of the centre with which the animal was born and with which it died. It was precisely the study of the respiratory centre that gave birth to all ideas of exact and constant localization of functions and revealed that the nervous centre should not be conceived as a small group of neurons always retaining constant properties. On the one hand, it became obvious that respiration also involved the spinal respiratory neurons, whose axons innervated the respiratory muscles. On the other hand, it was demonstrated that the groups of cells in the medulla oblongata, without which no rhythmic stimuli can originate in the efferent neurons of the respiratory muscles, were under the constant influence of the higher divisions of the brain.

Bulbar division of the respiratory centre. The aggregate of neurons in the medulla whose activity can ensure the rhythmic respiratory movements and whose destruction leads to a cessation of respiration is designated as the *bulbar division of the respiratory centre.*

The nervous structures connected with respiration do not take up all of the medulla, but only a relatively small portion of it (in the cat about 0.1 cm.^{3}) located, as was established by Mislavsky, in the reticular substance *(formatio reticularis).* This section is located in the dorsal division of the medulla between the level of the entrance of the 8th pair of cranial nerves and a line passing 2 to 4 mm. above the *calamus scriptorius* (Fig. 89). Stimulation of this section causes either an inspiration or an expiration; electric potentials originate in it in the act of respiration.

According to Mislavsky's increasingly confirmed ideas we should distinguish in the bulbar division of the respiratory centre neurons, whose stimulation leads to inspirations, and those, whose stimulation leads to expirations. By stimulating the medulla with contact electrodes it has been possible to show that the inspiratory neurons of the bulbar division of the respiratory centre lie in the ventral portion and the expiratory neurons in the dorsal portion of the reticular substance (Ranson et al.). These two regions are sometimes briefly referred to as the "inspiratory centre" and the "expiratory centre." Thus, the "inspiratory centre" implies the neurons whose excitation provokes inspiratory effort (through the spinal motoneurons which innervate the diaphragm, the external intercostals, etc.), while the "expiratory centre" signifies the neurons whose excitation stimulates expiration (also by affecting the corresponding motoneurons of the spinal cord).

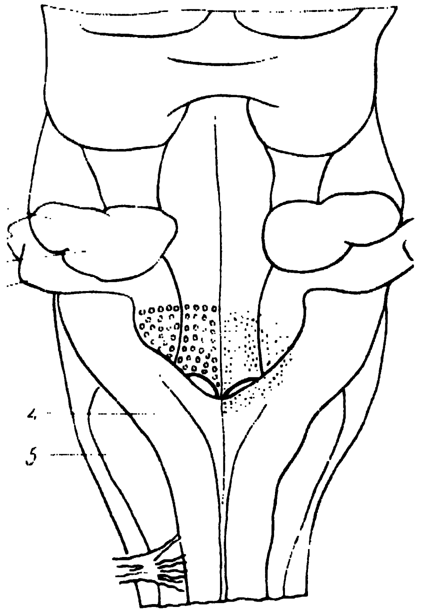

Fig. 89. Region of medulla oblongata, stimulation of which causes inspiration (dots), and region, stimulation of which causes expiration (circles) (after Ranson et al.).

brachium posterior; 2- brachium olfactorium corpus restiforme; 4- tuberculum acusticum ucleus cuneatus.

Between these morphologically separate groups of neurons of the bulbar divison of the respiratory centre there is an indissoluble functional connection owing to which expirations are inhibited during inspirations and vice versa.

The bulbar division of the respiratory centre and the spinal efferent neurons of the respiratory musculature are the stablest structures in the central nervous system as regards narcotics. This fact is very important to surgeons, because respiration is retained even when no other reflex reactions can be evoked in deep anaesthesia (true, so deep an anaesthesia can be easily replaced by a paralysis of the respiratory centre).

The fact that respiration can continue after removal of the entire cerebrum above the medulla should not mislead us to the conclusion that the respiratory centre is confined *only* to the medulla oblongata. The animals, in whom only the spinal cord and the medulla have been retained, cannot live for more than a few hours or days and die with symptoms of respiratory and circulatory disorders. Besides, the respiratory movements are frequently reduced to short and shallow inspirations each of which is immediately followed by an expiration with a protracted pause before the next inspiration. But if the vagi are cut in an animal deprived of the entire cerebrum above the medulla respiration easily stops during inspiration, i.e., the inspiration is no longer interrupted by an expiration.

Such an animal cannot very well adjust its respiration to changing environmental conditions (for example, changes in temperature) or to the changing conditions within the body itself (for example, muscular work).

It follows that the bulbar division of the respiratory centre is necessary for respiration, but is insufficient to ensure its normal control. Under normal conditions the respiratory centre is a complex whole of a number of nervous structures the lowest of which are controlled by subcortical and cortical neurons.

Subcortical and cortical structures of the respiratory centre. If we remove the cerebral hemispheres in the cat or the dog, but retain the midbrain and the cerebellum their respiratory functions continue for a longer time than when the medulla and spinal cord alone are retained. In this case individual investigators succeeded in keeping animals alive for a number of days by taking good care of them. The structures of the midbrain (and, perhaps, the cerebellum) probably exert an influence on the medulla which raises the excitability of the latter; owing to this the vitality of the animals in whom the midbrain has been retained is higher than in those in whom the medulla and the spinal cord have been separated from the midbrain.

However, respiratory control in animals deprived of the midbrain and the forebrain is very far from normal. Removal of the cerebral hemispheres deprives such animals of a good deal of their mobility and they, therefore, have no normal respiratory regulation during muscular work. They also show no respiratory changes in response to rises in the environmental temperature—the so-called thermoregulatory polypnoea is absent (Chapter 35).

The cerebral cortex takes part in the normal performance not only of all conditioned, but also of all unconditioned reflexes. The impulses originating in the receptors whose stimulation causes an unconditioned reflex reach definite sections of the cerebral cortex through a chain of neurons. Fibres leaving the cells of the cerebral cortex carry the excitation, originating in the cerebral cortex in response to the stimulation of the receptors, to the efferent neurons (with the aid of subcortical structures). The reflex arc of every unconditioned reflex, thus, normally involves the neurons of a number of divisions of the central nervous system, the cerebral cortex included.

The lower sections of the premotor zone of the cerebral cortex contain a mass of nerve cells which form part of the cortical division of the internal analyser (Chapter 68) and receive the impulses propagated to the central nervous system along the afferent fibres of the vagi; the impulses originating during stimulation of the pulmonary receptors are probably transmitted to these sections of the cerebral cortex. The same, and possibly also other, sections contain cells which receive the stimuli from the receptors of the aortic arch and the carotid sinuses whose stimulation plays an important part in the reflex stimulation of respiration.

The portions of the cerebral cortex, which are the higher instance reached by impulses from the receptors of the lungs, the large vessels, air passages and respiratory muscles, are the nervous structures involved in the performance of the unconditioned (inborn) respiratory reflexes in normal animals. They are, probably, the portions whose artificial stimulation by electrodes applied to the cortex regularly cause changes in respiration, as it was established by V. Danilevsky and later by V. Bekhterev, N. Mislavsky and a number of other investigators.

In addition to being involved in the unconditioned respiratory reflexes, the cerebral cortex is the organ in which the conditioned reflexes, always playing a part in the respiratory control in normal animals, come full circle. All the agents, which constantly coincide in time with unconditioned respiratory reflexes, acquire a capacity for changing respiratory activity by developing conditioned reflexes.

The *respiratory centre should,* thus, *signify the aggregate of all the structures in the central nervous system necessary and sufficient for normal control of respiration.* The idea of this centre cannot be confined only to a group of cells in the medulla oblongata.

Effect of CO_2 and of Oxygen Deficiency on Respiration

Hyperpnoea after withholding respiration and apnoea after hyperventilation. Simple observations show that respiration in man alters in response to chemical changes in the organism which result from disturbances in the normal gaseous exchange with the external environment. Suffice it to withhold respiratory movements for 20 to 30 seconds to have an uncontrollable desire to take a breath and make several vigorous respiratory movements. Withholding the breath, therefore, leads to subsequent rapid breathing—*hyperpnoea.*

Contrariwise, if respiration is voluntarily accelerated to the maximum for a period of 30 seconds to a minute the increased ventilation (*hyperventilation*) of the lungs will be followed by a much longer respiratory pause. There will be no need for any respiratory movements for 30 to 60 seconds. *Apnoea,* i.e., a cessation of respiration for lack of stimuli, results. It is impossible to withhold the breath for more than 30 to 60 seconds without a preceding hyperventilation. After hyperventilation the breath may be withheld for 1 to 2 minutes (there are significant individual differences, but the more vigorous the gaseous exchange the shorter the period of apnoea).

Carbon dioxide as respiratory stimulant. By causing a small rise in the partial pressure of oxygen in the alveolar air hyperventilation can increase its content in the blood but very little since even in ordinary respiration the arterial blood is normally almost saturated with oxygen. But hyperventilation sharply affects the content of CO_2 in the blood because the ensuing fall in the partial pressure of carbon dioxide in the alveolar air leads to the liberation of considerable amounts of CO_2 from the bicarbonates of the blood.

It is, therefore, natural to assume that hyperventilation is followed by apnoea because the content of carbon dioxide in the blood decreases. If this be true the increased amount of carbon dioxide in the blood must cause the opposite effect, i.e., it must lead to deeper breathing, to hyperpnoea. This is what actually occurs. If we add carbon dioxide to the inspired air respiration will become much more rapid. When inhaling air or oxygen containing 5 to 8 per cent CO_2 the volume of each inspiration and expiration may reach 2 to 2.5 litres, which with a simultaneous small acceleration in breathing leads to an increase in pulmonary ventilation of up to 40 to 60 litres per minute.

The same dependence is clearly revealed in the experiment with the so-called cross circulation for the first time conducted by Frédéricq. If we pass the blood of dog B into the head of dog A and either increase or decrease the carbon dioxide content in the blood of dog B dog A will show hyperpnoea in the former case and apnoea in the latter.

The nervous structures involved in the regulation of respiration are so sensitive to carbon dioxide that a rise of only 0.01 per cent in the content of carbon dioxide in the blood increases pulmonary ventilation by an average of 5 per cent (Haldane).

Owing to the fact that the respiratory centre is stimulated by an increase in the content of carbon dioxide in the blood its partial pressure in the alveolar air is maintained on quite a constant level. When the content of carbon dioxide in the blood increases and its tension, consequently, rises and more CO_2 is released into the alveoli the stimulation of the respiratory centre, caused by the increase in the content of CO_2 in the blood, leads to increased pulmonary ventilation. This results in a lowering of the partial pressure of carbon dioxide in the alveolar air. Contrariwise, with a fall of CO_2 tension in the blood less carbon dioxide is released into the alveoli (because of the lesser difference between the tension of CO_2 in the blood and its partial pressure in the alveolar air). When the CO_2 content in the blood decreases the respiratory centre is stimulated less and, consequently, respiration slows down and weakens. As a result the content of CO_2 in the blood increases again.

The reaction of the respiratory centre to the changes in the CO_2 content in the blood is, thus, a most important mechanism that maintains the constancy of carbon dioxide tension in the blood.

Inspiring a gas mixture containing 3 to 5 per cent carbon dioxide and 50 to 60 per cent oxygen is a good method for increasing pulmonary ventilation and oxygen supply to people poisoned by asphyxiating gases (for example, CO). In this case an increase in pulmonary ventilation is particularly important because it helps in the most rapid elimination of the poison from the organism.

Effect of carbon dioxide on respiration and significance of hydrogen ion concentration in the blood. An increase in the CO_2 content of the blood leads to a rise in the hydrogen ion concentration (p. 53) according to the equation:

$$[H^{\cdot}] = K' \frac{[CO_2]}{[HCO_3']} .$$

The production of acids stronger than carbonic acid displaces the latter from bicarbonates. Because of this the concentration of bicarbonates in the blood falls and the content of CO_2 rises. In addition, the concentration of

H-ions in the blood rises (in the above formula the numerator increases and the denominator decreases).

Because of this and owing to the fact that respiration becomes more rapid with the injection into the blood not only of CO_2, but also of any acid (for example, acetic, lactic, hydrochloric), a hypothesis was advanced that it was not the carbonic acid itself, but the hydrogen ions in the blood that stimulated respiration. It has been ascertained, however, that the influence of the various acids, injected into the blood, on respiration is much less constant than that of CO_2; besides, carbonic acid stimulates respiration with lower concentration of the H-ions in the blood than that at which the action of the other acids stimulating respiration becomes manifest. It is right to assume that carbonic acid as such is the natural and strongest (of the chemical agents) stimulant of the respiratory function. It is possible that this action is connected with the fact that CO_2 or the undissociated molecules of H_2CO_3 most easily penetrate into the nerve cells of the central nervous system and into the chemoreceptors.

We must also take into consideration that CO_2 is produced as a result of oxidative processes in the very nerve cells of the respiratory centre whose metabolism itself depends on the supply of oxygen and other substances with the blood.

Effect of oxygen deficiency on respiration. Oxygen deficiency of the blood also causes increased respiration. This is hard to appreciate by withholding the breath because it is accompanied by enrichment of the blood in CO_2 which is the strongest stimulant of respiration. But if a person breathes rarefied air at high altitudes or inspires a gas mixture poor in oxygen the conditions for eliminating carbon dioxide from the body change but little and the changes in respiration may be due only to oxygen deficiency. In this case it appears that already at the altitude of about 1,500 m. above sea level (and with a decrease in the oxygen contained in the inspired air to 17-18 per cent) respiration becomes more vigorous and pulmonary ventilation increases. However, with a fall of the oxygen tension in the blood pulmonary ventilation increases 2 to $2^1/_2$-fold at most, whereas with a rise of the carbon dioxide tension in the blood pulmonary ventilation may increase approximately eightfold.

Reflex Control of Respiration by the Chemoreceptors and Effect of Carbon Dioxide on the Respiratory Centre

Various reflexes, primarily in response to the stimulation of interoceptors, play a most important part in the regulation of respiration. Particularly important to the stimulation of respiration (in addition to the receptors in the lungs) (see below) are the impulses originating in the chemoreceptors located in the large blood vessels—in the already described aortic body of the aortic arch and in the carotid body of the carotid sinus (p. 164). *An increase of CO_2 and a decrease of oxygen in the blood stimulate the chemoreceptors in the aortic-carotid zone. This reflexly causes deeper and more rapid breathing* (Heymans et al).

Participation of the chemoreceptors of the aortic-carotid zone in the stimulation of respiration is demonstrated, in particular, by the fact that with a fall in the oxygen tension below 85 mm. Hg in the arterial blood the oscillograph registers accelerated impulses from the carotid nerve.

Respiration usually grows deeper and more rapid when blood rich in CO_2 is perfused through the vessels of various organs which maintain only a nervous connection with the whole organism (for method see p. 166). It follows that stimulation of the chemoreceptors located in the walls of all vessels and in all tissues may reflexly stimulate respiration (stimulation of these receptors sometimes inhibits respiration).

An animal with severed aortic and sinus nerves respiring air with low O_2 content shows no increase in pulmonary ventilation. Since in this case no impulses are transmitted from the chemoreceptors of the aortic arch and the carotid sinus to the centres the oxygen deficiency suppresses rather than increases respiration. The latter is due to the fact that the oxygen deficiency paralyzes the cells of the respiratory centre.

The foregoing facts show that the chemical changes in the blood—accumulation of CO_2 and oxygen depletion—affect the respiratory centre *reflexly*, by stimulating the chemoreceptors. At the same time an increase of carbon dioxide in the blood (or, probably, HCO_3 anions) may also directly stimulate the cells of the respiratory centre. This is demonstrated by experiments in which the respiration of animals increases when carbon dioxide accumulates in the organism even after the respiratory centre is disconnected from the receptors. This disconnection is made by cutting all the nerves entering the medulla and cutting the spinal cord below the medulla; the excitation of the respiratory centre after this operation is judged by the respiratory movements of the larynx and the *alae nasi*.

It has also been shown that respiration is increased by an injection of a drop of $NaHCO_3$ and H_2CO_3 buffer mixture into the region of the medulla, the contact electric stimulation of which provokes inspiration. An injection of a solution of acids into the same region does not produce this effect.

Lastly, it is well known that animals, in whom the nerves running from the receptors of the aorta and the carotid sinus have been cut, may retain relatively normal respiration.

The nerve cells of the respiratory centre may, consequently, be stimulated by the CO_2 of the tissue fluid which bathes them and into which the carbon dioxide passes from the blood.

B. Kravchinsky points out that in the lower vertebrates (fish and Amphibia) respiration ceases after severance of the vagi which contain afferent fibres from chemoreceptors corresponding to those of the carotid zone of the higher animals and from the receptors of the lungs (or of the branchiate apparatus). It is likely that the capacity of the nerve cells of the respiratory centre to be excited by the direct action of the carbon dioxide of the blood has developed in the process of evolution of the vertebrates.

Reflex Regulation of Respiration from the Pulmonary Receptors

The reflex regulation of respiration is not confined to the reflexes from the chemoreceptors of the blood vessels. Each respiratory act is reflexly regulated in the course of its performance by impulses originating in the receptors of the lungs and transmitted to the central nervous system along the vagal fibres which enter the medulla.

Fig. 90 (right) shows the effect of severing the vagus on respiration (Traube, 1847). As soon as the vagi are cut respiration becomes much deeper and slower. The pause between the respiratory movements is lengthened. This effect, as I. Pavlov ascertained, is retained for months and years, all through the remaining life of the vagotomized animal.

If we stimulate the proximal end of the vagus during an inspiration the most typical result will be a reflex interruption of the inspiration with an ensuing expiration (Fig. 90, left), while stimulation of the vagus during an expiration usually reflexly interrupts the expiration and produces an inspiration. These reflexes (named the *Hering-Breuer reflexes* after the investigators who discovered them in 1868) depend on the stimulation of the afferent vagal fibres which run from the receptors of the lungs.

A record of the contractions of an isolated slip of the diaphragm, the most important respiratory muscle (Fig. 91, top), shows that with the distention of the lungs (by air blown into them) the diaphragm relaxes, the inspiration is inhibited and a deep expiration occurs (experiment by Head). On the contrary, if we reduce the distention of the lungs, causing their collapse, the diaphragm contracts and an inspiration is stimulated. The greater the distention of the lungs during an inspiration the higher the frequency of the nerve impulses propagated from the pulmonary receptors along the afferent fibres of the vagus.

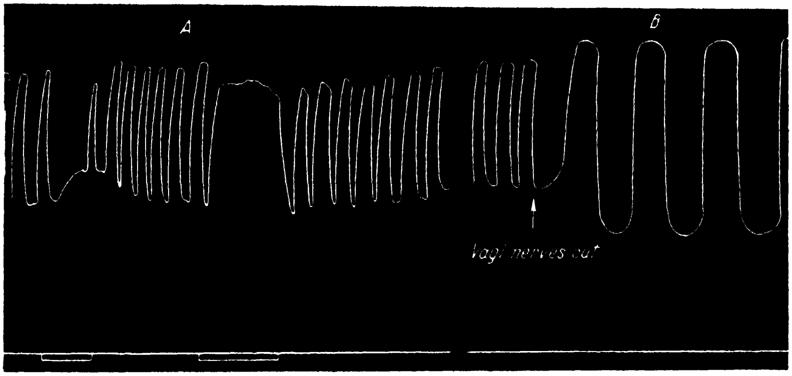

Fig. 90. Left half *(A)* shows effect of stimulation of distal end of vagus (its branch—laryngeal nerve) on breathing. Each rise in curve corresponds to inspiration, each drop to expiration. If nerve is stimulated at end of inspiration respiratory movements stop at inspiratory phase. If nerve is stimulated at end of expiration respiratory movements stop at expiratory phase. Right half *(B)* shows deepening and slowing of respiratory movements after severance of both vagi. Lower line marks stimulations.

It follows that ***an inspiration itself reflexly leads to its cessation and to an ensuing expiration.*** When the vagi are cut the impulses from the lungs no longer reach the respiratory centre, the inspiration is not interrupted reflexly and the respiratory movements become very deep (Fig. 90).

The bulbar division of the respiratory centre contains, as was pointed out, two groups of neurons—one group stimulating inspiration and the other—expiration. The reflex influence of the impulses propagated along the vagus from the pulmonary receptors to the respiratory centre may, therefore, be characterized as an influence inhibiting the inspiratory neurons of the bulbar division of the respiratory centre and exciting its expiratory neurons.

The results of the action of the afferent impulses from the receptors stimulated during inspiration depend on the state of the respiratory centre (N. Wedensky). M. Sergiyevsky has shown that the action of the impulses from the receptors of the lungs varies with the phase of respiration. In the beginning of the inspiration when the distention of the lungs only commences the impulses from the mechanoreceptors increase the inspiration, but as soon as a certain degree of pulmonary distention is reached, i.e., at a certain degree of excitation of the inspiratory neurons of the respiratory centre, the stimulation of the inspiration is replaced by its own reflex inhibition and reflex stimulation of the expiration ensues.

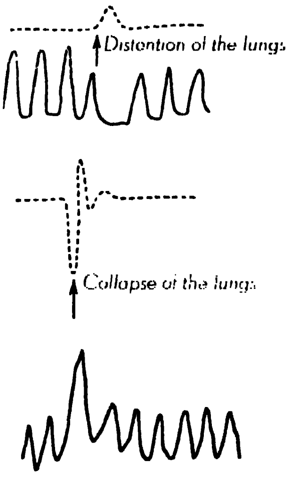

Fig. 91. Effect of distention and collapse of lungs on breathing.

Dotted line pressure in trachea (rise in line shows distention of lungs, drop collapse of lungs caused by pumping out of air). Continuous line shows movements of strip of diaphragm. Distention of lungs inhibits respiratory movements of the diaphragm; collapse of lungs produces opposite effect (after Head).

It is possible that a special group of mechanoreceptors stimulated during the collapse of the lungs exists. The reflex response from these receptors stimulated during expiration consists in inhibiting the active expiration and in stimulating an inspiration. Consequently, according to its cause and effect this reflex is opposed to that from the receptors stimulated during inspiration.

Normally severance of the vagi does not stop respiration, but only makes it deeper and slower. However, cutting the vagi in the dog with the brain stem severed in the region of the lower third of the pons Varolii results in a long inspiration which is frequently not interrupted by an expiration until the animal dies from asphyxia. Stimulation of the vagus during such an inspiratory halt interrupts the inspiration and leads to an expiration (Ranson, Pitts and Magoun).

On this basis some physiologists have concluded that the "centre" of inspiration is, presumably, always active and that the rhythm of respiration is due only to inhibitions of inspirations by impulses propagated along the vagus from the receptors of the lungs distended during inspirations or by impulses originating in the region of the upper half of the pons Varolii. This hypothesis has not been sufficiently substantiated and the idea of continuous activity of the "inspiratory centre" cannot, therefore, be accepted as yet. In the experiments involving the severance of pons Varolii the cutting itself may have caused a disproportionate activity of the neurons of the inspiratory division of the respiratory centre.

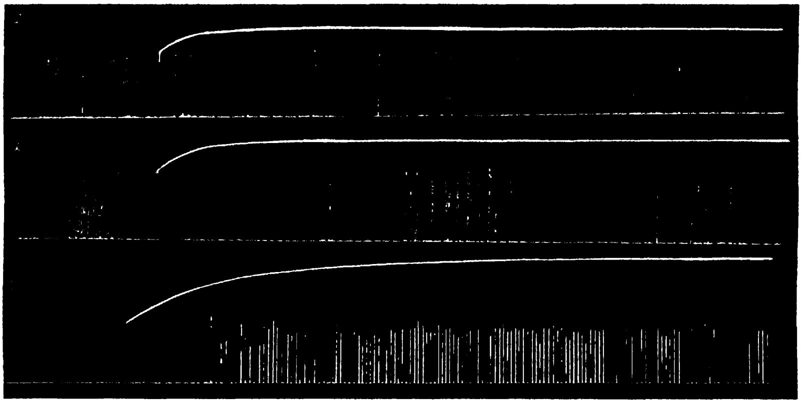

Fig. 92. Action currents in single afferent fibre of the cat's vagus during distention of lungs by blowing air into them.

The degree of lung distention is indicated in each record by white line over curve of bio-currents: *a*—5 ml. of air introduced into lungs, *b*—115 ml., *c*—230 ml. The greater the distention of the lungs the higher the frequency of bio-currents: *a*—80, *b*—120, *c*—250 per second (after Adrian).

Reflex influences from the receptors of the lungs play a most important part in maintaining the respiratory rhythm, the sequence of inspirations and expirations. In addition, the impulses from the pulmonary receptors not only inhibit inspiration, but may, under certain conditions, also stimulate respiration. Mislavsky thought so, the experiments of Sergiyevsky's associates favour this assumption, and it is also confirmed by observations which show that when respiration ceases because of a paralysis of the respiratory centre, rhythmic compressions of the thorax are the most efficient means for restoring independent respiration (V. Negovsky et al.).

Significance of impulses from the receptors of the respiratory passages and the respiratory muscles. In addition to the impulses from the receptors of the lungs a certain part in the regulation of respiration is also played by impulses from the receptors of the trachea whose stimulation during the passage of air through the latter variously affects respiration.

Contraction of the muscles which take part in respiration stimulates the receptors located in these muscles. Stimulation of the receptors of the inspiratory muscles reflexly predisposes to expiration, while stimulation of the receptors of the expiratory muscles reflexly predisposes to inspiration. The functional role of the reflexes from the receptors of the respiratory muscles is, consequently, similar to that of the reflexes produced by stimulating the receptors of the lungs, but is less pronounced.

Problem of Automatism of the Respiratory Centre

In 1863, I. Sechenov described a rhythmic generation of electric potentials in the medulla oblongata extirpated from the frog. This fact was confirmed much later by a number of investigators (Adrian et al.). Consequently, discharges of excitation rhythmically originate for some time in the isolated medulla and may be regarded as a manifestation of automatism of the respiratory centre.

The very brief experiments (because the isolated brain dies very rapidly) conducted for the purpose of ascertaining the automatism of the respiratory centre do not warrant any conclusions as to the significance of this phenomenon under normal conditions. It is possible that automatism manifests itself precisely because of the artificial conditions of the experiment, due to the stimuli originating at the points where the nerves and the brain were cut and owing to the impossibility of normally removing the waste products of tissue metabolism from the cells.

The automatism of the respiratory centre may, possibly, be connected with the fact that the central nervous system is capable of rhythmic stimulation in the same rhythm in which the impulses from the receptors acted on these centres directly before.

We saw that the impulses originating from the receptors of the lungs during inspirations and expirations played an important part in regulating the respiratory rhythm. A certain rhythm of activity, a certain rhythm of cyclical chemical reactions occurring in it, is forced, as it were, on the respiratory centre by the pulmonary receptors stimulated during inspiration and expiration.

There are facts indicating that this rhythm of impulses may for some time be retained by the respiratory centre also after cessation of its rhythmic stimulation from the receptors. This is apparent, for example, from the following fact: when respiration is maintained for a long time by a rhythmic insufflation of air into the lungs during a temporary paralysis of the respiratory centre, or in curare poisoning, normal respiration adopts the same pattern for some time after its restoration.

Conditioned Reflexes Regulating Respiration

Stimulation of the respiratory centre by the carbon dioxide of the blood acting on the chemoreceptors and on the nerve cells of the central nervous system, as well as the stimulation of this centre by the impulses from the receptors of the lungs and the entire respiratory apparatus, is an inborn mechanism for the regulation of respiratory activity. These stimuli result in respiratory movements which rhythmically follow one another even when the normal function of the higher divisions of the brain is discontinued as, for example, in deep anaesthesia. Under these conditions the reflex activity of the bulbar division of the respiratory centre may for some time keep up the respiratory movements.

Under normal conditions, however, the higher divisions of the brain, the cerebral cortex included, always take part in regulating respiration.

The impulses transmitted to the medulla oblongata from any receptors, including the chemoreceptors of the aortic-carotid zone and the pulmonary receptors, affect the cerebral cortex. Any agent which precedes inspiration of a mixture of air with 4 to 8 per cent carbon dioxide becomes a conditioned respiratory stimulus. After removal of the cerebral cortex inspiration of carbon dioxide (3 to 5 per cent of the inspired air) increases respiration less than it does normally, while during inspiration of carbon dioxide the change in the excitability of the motor zone of the cerebral cortex occurs before any respiratory changes (Sergiyevsky). Stimulation of the afferent vagal fibres alters the excitability of the cerebral cortex.

The impulses originating during muscular activity in the mechanoreceptors and the chemoreceptors of the skeletal muscles and tendons are natural conditioned stimuli of respiration. These impulses act on the cerebral cortex simultaneously with the accumulation of carbon dioxide in the blood and the depletion of the latter in oxygen produced by hard work; the excitation of the cortical divisions of the respiratory centre produced by the action of carbon dioxide coincides with that from the receptors of the motor apparatus. A temporary bond is formed; this bond is extremely strong, as strong as all temporary bonds which produce the natural conditioned reflexes.

Due to the development of conditioned reflexes the stimuli which of themselves have nothing to do with respiratory innervation now exert a considerable influence on it. This is of particular importance in muscular activity. If the latter is not very vigorous the blood usually shows no changes in CO_2 tension which might cause an appreciable increase in respiration that accompanies muscular work. During hard muscular work pulmonary ventilation reaches 100 to 110 litres per minute, i.e., exceeds the maximal pulmonary ventilation provoked by inspiration of carbon dioxide by about 50 per cent. It follows that during work respiration is stimulated not only, and not so much, by the inborn lower mechanism of regulation of respiratory activity; the latter normally always includes conditioned-reflex influences. Their development, as has just been said, can be explained by a rapid development of respiratory conditioned reflexes. When such conditioned reflexes have developed and muscular activity has itself become a signal for increased breathing, the importance of its direct inborn stimulation may recede into the background. This is the result of the aspect of conditioned-reflex activity due to which the effect based on cortical stimulation may exceed the effect of the unconditioned reflex.

The increase in pulmonary ventilation during passive flexion and extension of the extremities which lead to stimulation of the muscle receptors without essential changes in the total metabolism confirms the fact that stimulation of the muscle receptors stimulates respiration as a result of the development of a conditioned reflex (M. Marshak et al.).

The rhythmic respiratory movements during muscular rest also, probably, depend on *time reflexes*.

The time reflexes manifest themselves, for example, as follows: if a dog is fed at strictly definite intervals of time, towards the end of the interval between the feedings the dog begins to secrete saliva and show other signs of food reaction. The interval of time between the two stimuli becomes a conditioned stimulus because a certain unconditioned reflex always follows at the end of the given interval.

In the rhythmic sequence of inspirations and expirations an enormous part is played, as we have seen, by impulses from the pulmonary receptors. These impulses undoubtedly also reach the cerebral cortex. There is every reason to believe that the impulses of the pulmonary receptors acting as unconditioned stimuli serve as the basis for the development of a conditioned reflex to the intervals of time which usually separate these impulses from each other. The old observation made by Pavlov before he had begun working on conditioned reflexes proves this contention. In studying the chances for dogs to survive the severance of both vagi, I. Pavlov found that the respiratory movements growing slower immediately after the vagi have been cut and going down to 8 or 9 respirations per minute continued growing slower after the operation. Three to four weeks after the vagotomy the dog made only 4 to 5 respirations per minute. This can be explained by the fact that for some time after the operation the conditioned reflexes developed by the stimulations of the pulmonary receptors were retained, whereas a long time after the operation these conditioned reflexes faded because they were no longer supported.

Normal regulation of respiration is, thus, conditioned by cortical mechanisms which form a single whole with the inborn unconditioned reflexes and lead to complex-reflex respiratory acts in which unconditioned and conditioned reflexes are most closely interwoven.

Respiratory Changes Under the Action of Various Stimuli

Effect of changes in blood pressure and of stimulation of the upper respiratory passages on respiration. In addition to the influences from the chemoreceptors of the carotid sinus the respiratory centre is also affected by the impulses from the baroreceptors of the aortic-carotid zone which play a very important part in regulating the blood pressure. A lowering of the blood pressure in the aortic-carotid zone stimulates respiratory activity, while a rise in the blood pressure temporarily stops respiration or slows it down.

Effect of pain stimuli on respiration. A short pain stimulus will at first cause a brief cessation of respiration (sometimes after a deep inspiration). A longer pain stimulus usually provokes deeper, more vigorous and faster respiratory movements. However, protracted pain stimulation sometimes depresses respiratory activity.

Effect of stimulation of the receptors of the upper respiratory passages on respiration. Strong stimulation of the sensitive endings of the trigeminal nerve in the nasopharyngeal mucosa (for example, when ammonia is inhaled) usually stops the respiratory movements reflexly for 10 to 20 seconds. A weaker stimulation of the nasal mucosa (for example, by clots of mucus, dust) causes a deep inspiration followed by a very strong and fast expiration with the mouth closed (sneeze).

Stimulation of the receptors of the tracheal and bronchial mucosa reflexly evokes a strong inspiration with a simultaneous narrowing of the glottis. This causes air currents to be driven out of the lungs under considerable pressure (cough) which aids in eliminating the particles irritating the air passages. These coughing movements can be provoked experimentally by stimulating the proximal end of the upper laryngeal branch of the vagus.

Cheyne-Stokes or periodic respiration. This abnormality is characterized by the fact that several, sometimes increasingly deep, respirations are followed by a respiratory pause lasting 5 to 10 seconds and longer. The cycle is repeated over and over again.

Cheyne-Stokes respiration is usually due to decreased excitability of the respiratory centre. The respiratory centre is stimulated only when the content of oxygen in the blood sharply falls owing to a very long respiratory pause. This provokes a few respiratory movements resulting in an increase in the oxygen content of the blood which again produces a long respiratory pause lasting until the oxygen deficiency makes itself felt again.

Cheyne-Stokes respiration is a symptom of a derangement in the activity of the respiratory centre (however, it also occurs sometimes in healthy people). Such a change in respiration may be caused by preceding hyperventilation; during the apnoea that follows the oxygen content of the blood sharply decreases while the content of CO_2 has not yet become normal. Several respiratory movements leading to an increase in the oxygen content of the blood occur but, since there is still little CO_2 in the blood, respiration ceases after several inspirations again until an oxygen deficiency is experienced, etc. Inspiration of oxygen, therefore, frequently relieves Cheyne-Stokes respiration.

Cheyne-Stokes respiration may also result from superficial breathing because the latter is responsible for the insufficient supply of the blood with oxygen and for the oxygen hunger of the cells of the respiratory centre, which disturbs their normal function. Superficial breathing may be the result of excessive reflexes from the pulmonary receptors. Such excess of these reflexes considerably shortens the inspiration which is interrupted very soon after its beginning; the same occurs with the expiration which is interrupted by an inspiration.

In disorders of the function of the respiratory centre breathing in a horizontal position is often more difficult than in the standing or sitting postures. This symptom is called *orthopnoea* and is partly due to the fact that in a horizontal position the abdominal organs interfere with the movements of the diaphragm.

Respiratory Control During Muscular Activity

Regulation of respiration during muscular activity, which is always accompanied by an increase in pulmonary ventilation due to deeper and faster respiratory movements, is based on complex-reflex mechanisms, involving various conditioned reflexes.

Muscular activity involves stimulation of a number of interoceptors: receptors of the muscles (and their tendons) contracting during a given type of muscular work, labyrinthine receptors, cardiac receptors whose activity always varies in muscular work, etc. In the course of life the stimulation of these interoceptors in their various combinations constantly combines with the influence of agents which call forth inborn, unconditioned reflexes (effect of CO_2, stimulation of the pulmonary receptors). This gives rise to different natural conditioned reflexes which influence the process of respiration (these reflexes always combine with cardiovascular conditioned reflexes) the conditioned stimulator of which is a complex of stimuli of the just mentioned (and other) interoceptors. Light work influences blood chemistry but little and the increase in respiratory movements is due mainly to the stimulation of the receptors of the contracting muscles.

Not only positive, but also inhibitory conditioned reflexes decreasing the rapidity and depth of respiration may be developed for the latter; inhibitory conditioned respiratory reflexes may, in particular, play a part in fixing the thorax during a number of static muscular efforts.

Muscular work also stimulates several exteroceptors which in turn leads to development of conditioned respiratory reflexes. The circumstances under which work is usually done, the time of day connected with considerable muscular activity, the landscape in which it is performed (for instance, a landscape for mountain-climbers) are all transformed into a complex pattern of stimuli connected with various modifications of the respiratory function and, therefore, producing conditioned-reflex changes in respiration.

It is only this respiratory regulation on the part of the cerebral cortex that makes possible, for example, an increase in pulmonary ventilation of up to 100 or 120 litres of air per minute during maximal muscular work, whereas during inspiration of carbon dioxide, formerly considered the most powerful and universal stimulator of respiration, pulmonary ventilation never exceeds 50 to 70 litres per minute. This shows that during work increased respiration is determined by various conditioned reflexes which merge with the inborn mechanisms of respiratory regulation and permit the fine adjustment of respiration to the nature of muscular work and the conditions under which it is done.

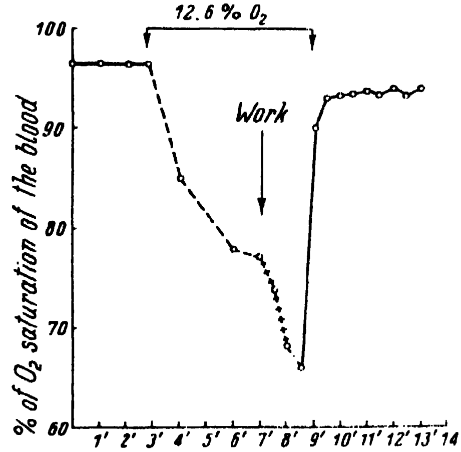

Fig. 93. Drop in oxygenation of blood during inspiration of gas mixture containing only 12.6 per cent oxygen and in muscular work (after M. Marshak).

Cortical stimuli are of similarly great importance in the regulation of respiration during changes in the external temperature (Chapter 35).

Under normal conditions and even during hard muscular work the blood is nearly fully oxygenated in the lungs. But if the partial pressure of oxygen in the inspired air drops, as it occurs when the breath is withheld and when air deficient in oxygen is inspired (Fig. 93), the oxygenation of the blood during muscular work decreases sharply.

CHAPTER 23

HYPOXIA AND EFFECT OF ALTERED ATMOSPHERIC PRESSURE ON THE BODY

Classification, Cause and General Characteristics of Hypoxia

Any oxygen deficiency in individual tissues or in the body as a whole is referred to as *hypoxia*. In a number of cases hypoxia is due to an oxygen deficiency in the blood and is then called *hypoxemia*.

Hypoxia may be caused by an insufficient oxygenation of the blood in the lungs. In this case we have the so-called *respiratory hypoxia* which is conditioned by: a) an oxygen deficiency in the inspired air, b) an affection of the pulmonary tissue (for example, in pneumonia or in poisoning with certain gases) and c) impairment of respiratory regulation.

Hypoxia may result from an insufficient flow of blood to an individual organ or to a slowing down and cessation of circulation as a whole. This type of hypoxia is designated as *circulatory hypoxia* (any death caused by a stoppage of the heart is essentially death from hypoxia).

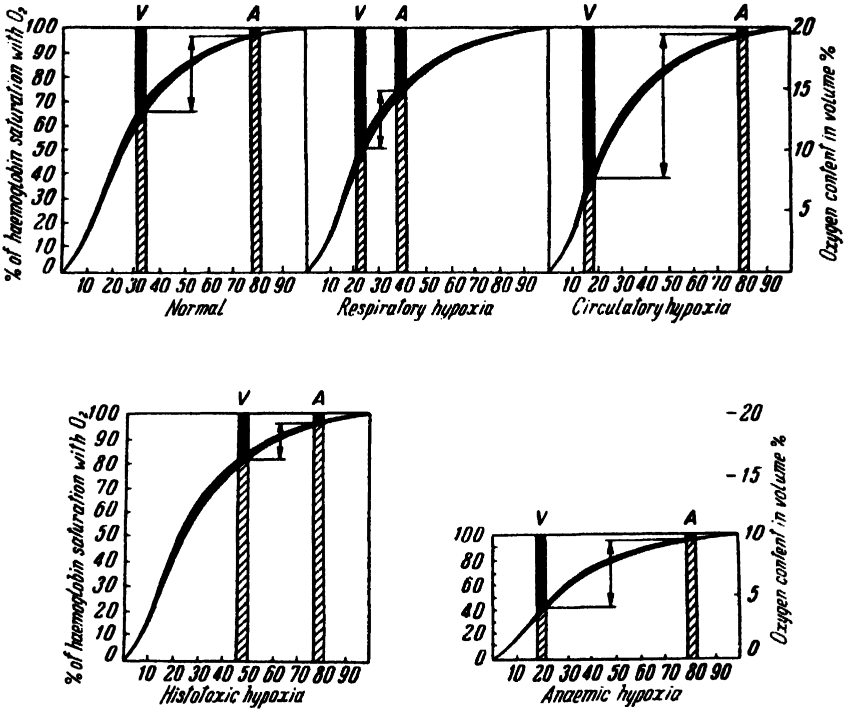

Fig. 94. Change in conditions of oxygen transport in various forms of hypoxia.

Each diagram shows oxygen dissociation curve: left scale — % haemoglobin oxygenation, and right scale — absolute oxygen content in blood. Columns show oxygen content (in % of oxygen capacity of blood and — on right scale — absolute figures in arterial (*A*) and venous (*V*) blood). Shaded part of columns — undersaturation of blood with oxygen. Arrows pointing in opposite directions — arteriovenous difference. Diagram of anaemic hypoxia is lower because in this form of hypoxia haemoglobin content of blood is reduced (after van Liere).

Hypoxia may be due to a deficiency of blood in the organism (*anaemic hypoxia*) or to changes in the blood owing to which the latter cannot transport sufficient oxygen (this occurs when haemoglobin changes to methaemoglobin or when its atom of iron is blocked by carbon monoxide).

Hypoxia may also be produced by an impaired capacity of the tissues to bind oxygen which may be a result of poisoning, for example, by hydrocyanic acid (so-called *histotoxic hypoxia*).

The various forms of hypoxia are illustrated in Fig. 94. This figure shows that in respiratory hypoxia the arterial blood contains less oxygen, while in circulatory hypoxia it is the venous blood that contains much less oxygen (since in this case the blood flows through the tissues slower than normal and gives off more oxygen to the tissues); the oxygen tension is, therefore, also sharply reduced in circulatory hypoxia; in slight respiratory or anaemic hypoxia the acceleration of circulation in some measure compensates for the decrease of O_2 per unit of volume of the arterial blood. In histotoxic hypoxia the O_2 tension in the venous blood is higher since the tissues cannot normally take the oxygen from the blood.

With the exception of circulatory hypoxia, which is due to a decrease in the blood flow to individual organs, the other forms of hypoxia lead to an insufficient oxygen supply of *all* tissues. But since the sensitivity of various tissues to oxygen deficiency differs the same degree of hypoxia may affect some organs more than others.

Sensitivity of various tissues to hypoxia. The higher divisions of the central nervous system and the higher receptors (for example, the retina) react more than any other organ to an oxygen deficiency, as, in general, to any changes in the internal environment. This becomes especially evident in acute hypoxia. In this case fainting may supervene immediately, as it occurs, for example, when blood supply to the cerebrum fails or when a gas mixture containing less than 4 to 5 per cent oxygen is inhaled. If fatal hypoxia develops slower its initial phase manifests itself in a sort of intoxication, in the loss of proper orientation in the surroundings. Disturbances in the normal supply of oxygen to the brain cause characteristic disorders of the conditioned reflexes (p. 229). Frequently no subjective disorders are observed in this case; the subject feels elated (euphoria), but this is due to the impaired ability to orient himself in the surroundings (for example, highly skilled physiologists subjected themselves to hypoxia for the sake of experiment and could not properly turn the tap in the instrument they themselves had devised). Owing to the impairment of the functions of the higher divisions of the brain even those who were specially warned about the consequences of oxygen deficiency are not aware of the mortal danger which arises in hypoxia. If hypoxia is aggravated the phase of euphoria is immediately followed by coma (paralysis of the higher functions of the cerebral cortex). The paralysis of the higher functions of the cerebral cortex is followed by a paralysis of the subcortical centres, the centres of the interbrain, the midbrain, the medulla oblongata and, finally, the spinal cord. Respiration is paralyzed and death ensues.

Irreversible changes occur in the cerebral cortex if the brain is fully deprived of oxygen (for example, in strangulation, in occlusion of cerebral vessels) for 5 to 6 minutes. After 5 minutes of complete hypoxia caused by strangulation or cardiac arrest (clinical death) dogs can be revived by artificial respiration and by pumping oxygenated blood into their arteries. For the rest of their lives, however, these dogs behave like animals with a removed or gravely diseased cerebral cortex (E. Asratyan, I. Petrov, V. Negovsky).

The kidneys, the liver and the heart muscle are somewhat less sensitive to oxygen deficiency, but disorders of their functions in hypoxia never fail to manifest themselves. Considerable local hypoxia, for example, during occlusion of the hepatic, renal or coronary arteries rapidly leads to paralysis of the functions of these organs.

Paralysis of the functions of the skeletal muscles occurs within several minutes after the occlusion of their vessels, but the muscles do not lose their vital activity soon and regain their efficiency shortly after restoration of circulation.

Changes in Metabolism During Hypoxia

Before hypoxia has reached and advanced the rate of basal metabolism (gaseous exchange) and the energy output it determines do not undergo sharp changes. This is due to a number of changes in respiration and circulation as a result of which the supply of the tissues with oxygen is almost normal. In this case, however, the amount of oxygen transported to the tissues in a unit of blood volume diminishes and the retention of oxygen consumption at the normal level is due to an increase in the splitting of oxyhaemoglobin and in the quantity of blood flowing to the tissues (except in histotoxic hypoxia). The greater use of the oxygen of the arterial blood by the tissues decreases the content of oxyhaemoglobin in the venous blood flowing from the tissues (hence, the cyanosis).

It was but recently believed that the oxygen exchange in the tissues altered in hypoxia only when the amount of oxygen received was insufficient to cover its consumption. It was, therefore, thought that in moderate hypoxia the oxygen exchange did not alter. Actually, the constancy of the gaseous exchange (by far not always observed in hypoxia) is not due to the fact that hypoxia does not affect metabolism, but is a result of regulatory adjustments which ensure the maintenance of a certain constancy of metabolism despite the effect of hypoxia. This is demonstrated by the fact that in certain cases of hypoxia in man and constantly in mountain animals acclimatized to high altitudes (for example, in sheep kept in the mountains for several generations) the total consumption of oxygen diminishes. The diminution of the oxygen exchange in hypoxia is observed only in adult animals; it does not occur, for example, in lambs. It follows that reflex influences leading to a decrease in the metabolism develop during the individual's lifetime (Slonim and Olnyanskaya).

Respiratory and Circulatory Changes in Hypoxia

A drop in oxygen tension in the blood at first always results in *greater* activity of the respiratory centre which is responsible for the acceleration and deepening of respiration at rest and, especially, during muscular work. This effect is due mainly to the reflex stimulation of the chemoreceptors of the aortic arch and the carotid sinus. The increase in pulmonary ventilation even leads to a pH increase in the blood because the latter loses a large amount of carbon dioxide. With the receptors of the aortic arch and the carotid sinus inhibited hypoxia does not increase respiration, and paralysis of the respiratory centre ensues without the phase of its intense activity.

Increased activity of the respiratory centre and, consequently, increased pulmonary ventilation are characteristic of hypoxia in its early stages. It benefits the body when hypoxia is caused by insufficient arterialization of the blood in the lungs (respiratory hypoxia). In this case the increase in the pulmonary and, consequently, in the alveolar (p. 194) ventilation, leading to a rise in the partial oxygen pressure in the alveolar air, increases the oxygenation of the blood. In other forms of hypoxia, which are not due to oxygen deficiency in the arterial blood, the increase in respiratory activity cannot aid in relieving hypoxia.

With an aggravation of hypoxia the efficiency of the respiratory centre falls, at first manifesting itself in Cheyne-Stokes and superficial respiration which does not provide sufficient pulmonary ventilation. In this case insufficient respiration is added to the causes of hypoxia resulting in a vicious circle: hypoxia, which at first caused an increased activity of the respiratory centre, subsequently leads to its insufficient activity and the resulting respiratory insufficiency aggravates hypoxia still more. This circle can be broken only by eliminating the causes of hypoxia, inspiration of oxygen being the best method. Hypoxia of the respiratory centre disappears and the latter resumes its normal functioning.

The circulatory changes in hypoxia are characterized by a fast heart rate, an increase in the minute volume of the heart and a certain rise in the arterial blood pressure. The mass of circulating blood increases owing to the emptying of the blood depots; the vessels of the abdominal organs contract. Because of this more blood flows to the tissues per unit of time. The increased blood supply to the tissues is an important means for providing them with enough oxygen despite the fact that its content per unit of blood volume is lower. As long as the mechanisms of circulatory regulation are not impaired in hypoxia its reflex devices cause an increase in blood supply to the heart and the brain and this provides the nervous centres with sufficient oxygen.

However, two phases are noted both in hypoxia and in respiratory regulation. The first phase has just been described. The second phase is characterized by its opposite effect since it is conditioned by an impairment of the vasomotor centres in advanced hypoxia. In this case the pulse becomes fast and irregular and hardly palpable. the blood pressure falls and the amount of blood flowing to the brain diminishes. A vicious circle is produced again: advanced hypoxia causes circulatory disorders and these lead to a further decrease in the blood supply to the brain. Coma and death rapidly ensue.

Mechanism of Changes in Hypoxia

In all cases of hypoxia. even during the period when neither the oxygenation of the arterial blood nor the rate of the oxygen exchange have altered, the tension of the oxygen dissolved in the blood and, consequently, in the tissues falls. The drop in the tissue oxygen tension is the earliest form of response to hypoxia. This often very rapidly combines with the effect of the changes in the composition of the blood conditioned by such alterations in metabolism as are a direct result of hypoxia.

In the initial phase of hypoxia the changes in physiological functions are conditioned by reflex acts resulting from the stimulation of the chemoreceptors in the aortic-carotid zone and in other tissues.

The fall of the oxygen tension in the tissues and the vessels of the internal organs and the accumulation, in this connection, of metabolites in the tissues lead to the stimulation of the vascular and tissue chemoreceptors. The impulses from these chemoreceptors reflexly alter respiration, circulation and, presumably, metabolism as well.

The reflexes produced in hypoxia by the stimulation of the chemoreceptors combine with the reflexes originating from the baroreceptors and the mechanoreceptors of the organs whose functions are altered by hypoxia. New reflex changes arise and in their turn affect the body. The changes of various functions conditioned by hypoxia are, thus, the sum total of a number of reflexes produced by the stimulation of numerous receptors. In advanced hypoxia all functions of the body are affected by the changes in the functional state of the central nervous system, primarily of the cerebral cortex resulting from the insufficient supply of oxygen to the nerve cells and their reactions to the changes in the composition of the blood and the flow of impulses from the various receptors stimulated in hypoxia.

The unconditioned reflexes produced by hypoxia combine and form a single whole with the conditioned reflexes originating from all the stimuli which coincide in time with the effect of hypoxia. It has been shown, for example, that the stimuli which had preceded the development of hypoxia produced qualitatively the same increase in respiration as did oxygen deficiency.

Changes in the activity of the cerebral cortex in hypoxia affect all functions of the organism. These changes are reflected in the electro-encephalogram (Chapter 60).

Effect of Rarefied Air on the Body

The higher the altitude the lower the partial pressure of oxygen in the inspired air, which leads to a drop in this pressure in the alveoli and, as a result, to a fall in the oxygen tension in the arterial blood.

The arterial blood (see Fig. 84) is approximately 95 to 90 per cent oxygenated as long as the barometric pressure holds above 500 to 550 mm. Hg, which corresponds to 3 to 3.5 km. above sea level. With the subsequent fall of the barometric pressure the oxygenation of the arterial blood rapidly decreases going down to 50 per cent of its oxygen capacity at the barometric pressure of 270 to 300 mm. Hg (about 7.5 to 8 km. altitude).

Table 7

Barometric Pressure, Partial Oxygen Pressure in the Inspired and in the Alveolar Air and the Percentage of the Arterial Blood Oxygenation at Different Altitudes

Altitude (in km.) above sea level	Barometric pressure (in mm. Hg)	Partial pressure of oxygen in inspired air (in mm. Hg)	Partial pressure of oxygen in alveolar air (in mm. Hg)	Percentage of oxygenation of arterial blood (in % of oxygen capacity)*
0	760	159	105	95
2	600	125	70	92
4	460	98	50	85
6	355	74	40	70
8	270	56	30	50
9	230	48	Below 25	20-40
11	170	36	—	Close to 0

Physiological changes at high altitudes. Most people ascending to an altitude of 2.5 to 3 km. above sea level do not suffer serious discomforts. This does not mean, of course, that at an altitude of 1.5 to 2 km., especially of 3 km. above sea level, the body is in the *same* state as at sea level barometric pressure. Though the arterial blood is still oxygenated to at least 90 per cent of its oxygen capacity at the altitude of 1.5 to 2 or 3 km. the *tension of the oxygen dissolved* in the blood is reduced and this conditions a number of changes in the organism, which include: a) a deepening and slight acceleration of respiration, b) an acceleration of the pulse rate and an increase in the minute volume of the heart, c) a certain increase in the mass of the circulating blood, d) an increased production of erythrocytes (during a long stay at high altitudes) and e) a slight (detected only by very fine methods) decrease in the excitability of the receptors which disappears after 2 or 3 days of staying at this altitude.

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* This column gives only approximate figures since the corresponding values depend on a number of factors: the rate of pulmonary ventilation, the carbon dioxide tension and the nature of the oxygen dissociation curve.

These changes are actually regulatory processes normally ensuring the maintenance of efficiency at the given altitude. A stay in the mountains at an altitude of 1 to 2 km. above sea level is sometimes even used as a therapeutic method in fighting certain diseases.

Disorders of a number of functions begin to manifest themselves at an altitude of 3 to 3.5 km. above sea level: these are due mainly to changes in the normal activity of the higher centres. At this altitude it is not only the tension of the oxygen dissolved in the blood that decreases, but also the amount of oxygen bound by haemoglobin that diminishes. More or less grave symptoms of respiratory hypoxia usually appear when the oxygenation of the arterial blood falls below 85 to 80 per cent of the oxygen capacity of the blood. But a drop in the oxygenation of the arterial blood below 50 to 45 per cent of its oxygen capacity is fatal to a human being suffering from respiratory hypoxia.*

The symptoms of slowly developing hypoxia are: fatigue, apathy, somnolence, finger tremor, headaches, short breath and tachycardia, frequent nausea, sometimes haemorrhages ("altitude" or "mountain" sickness); these symptoms do not appear in rapidly developing hypoxia because the higher functions of the brain soon cease and coma ensues.

Changes in the higher nervous activity may begin even before the amount of oxyhaemoglobin in the blood has diminished depending on the fall in the tension of the blood-dissolved oxygen. In dogs (experiments performed by M. Brestkin) certain changes in the higher nervous activity are noted already at an altitude of 1,000 to 2,000 m.; these changes manifest themselves first in increased conditioned reflexes and weakened inhibitory processes in the cerebral cortex. At higher altitudes the conditioned reflexes diminish and then disappear (at an altitude of 6 to 8 km.). The unconditioned reflexes also diminish. Inhibition grows stronger in the cerebral cortex. Whereas at low altitudes (2 to 4 km.) changes in conditioned reflexes are noted only in the beginning, at high altitudes disturbances in the conditioned reflex activity during long-continued hypoxia increase rather than diminish.

The changes in the states of the cerebral cortex produced by hypoxia affect all physiological functions. Inhibition developing in the cortex may spread to the subcortical structures impairing motor acts and strengthening the reflexes in response to impulses from the interoceptors.

Limit of altitude tolerance. Depending on the individual peculiarities of the body and its acclimatization the altitudes at which grave and then fatal disorders appear differ, but different as these altitudes may be everybody is infallibly affected.

The following average scale of altitudes at which definite functional changes appear may be indicated for healthy people:

a) up to an altitude of 2.5 to 3 km. most people (some people up to 3.5 to 4 km.) suffer no appreciable discomfort. The oxygenation of the blood is still above 85 per cent of its oxygen capacity and the only functional changes observed are an increased activity of the respiratory and cardiovascular systems and an increased erythropoiesis;

b) the following disorders of the higher nervous activity and of respiratory and circulatory regulation begin to appear at an altitude of 4 to 5 km.: euphoria or, on the contrary, depression lassitude, Cheyne-Stokes respiration, sharp increase in pulse rate and sometimes collapse;

c) at an altitude of 6 to 7 km. these symptoms become very grave for most people except the specially acclimatized;

d) staying at an altitude of 7 to 8 km. always leads to serious consequences and is dangerous to most people, while the altitude of 8.5 to 9 km. is the limit above which no human being can rise (without inspiring oxygen).

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* Considerable underoxygenation of the blood is observed in animals constantly living in the mountains. For example, in sheep at an altitude of 4,000 m. above sea level the blood is oxygenated to only about 65 per cent of its oxygen capacity though they show no pathological symptoms of hypoxemia (A. Ginetsinsky).

Acclimatization to Hypoxia

Increased resistance of the body to oxygen deficiency is referred to as acclimatization to the effect of rarefied air. This *altitude acclimatization* is achieved by the action of a number of factors.

During acclimatization erythropoiesis increases, the number of erythrocytes reaching 7 to 8 million per mm.^{3} of blood instead of the normal 4.5 to 5 million. The content of haemoglobin in the blood increases and its oxygen capacity rises to 22 volume per cent instead of the usual 17 or 18.

The oxygen dissociation curve shifts to the left so that at a low tension the oxygen in the alveolar air more easily combines with the haemoglobin and at the same time with the low partial pressure the oxygen in the tissues splits off from the oxyhaemoglobin with greater difficulty. It is still not quite clear whether or not this shift of the dissociation curve is in the long run a factor that improves the supply of the tissues with oxygen (some studies noted a shift of the oxygen dissociation curve to the right during prolonged acclimatization to high altitudes).

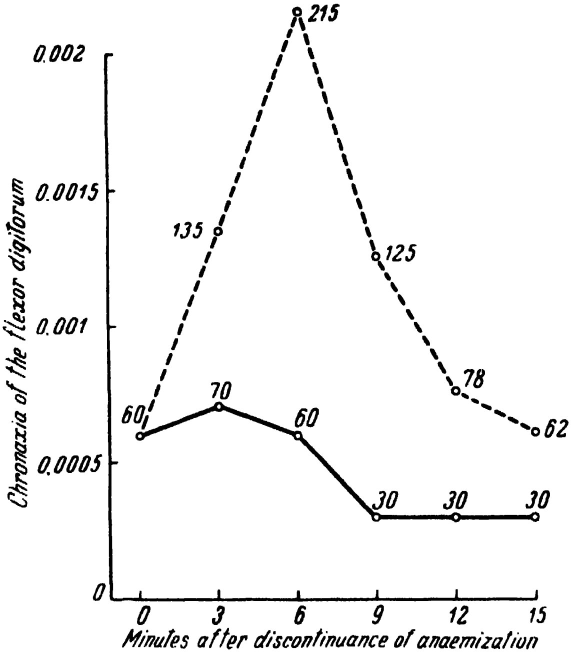

Fig. 95. Change in reaction of tissues to anaemization after several repetitions.

Diagram shows changes in chronaxie of common flexor digitorum after anaemization, which lasted 15 minutes, was discontinued (anaemization was caused by inflation of a cuff, placed on the shoulder, to 200 mm. Hg). Dotted line— postanaemic changes in chronaxie before series of repeated anaemizations (average of three experiments). Continuous line same changes after 15-minute anaemizations of arm were performed twice daily over period of one month. Figures over curves show chronaxie values in hundred thousandths of a second (from data by L. Filatova and G. Konradi)

The increased erythropoiesis, the greater oxyhaemoglobin content and the change in its dissociation curve appear quite tardily (after several days or 1 to 2 weeks staying at high altitudes) and disappear just as slowly after descent to the sea level, but changes in pulmonary ventilation, in the heart rate and in the minute volume of the heart occur immediately and are the most important means of increasing the oxygen supply to the tissues during a fast ascent to a high altitude. As the altitude acclimatization develops cardiac activity and pulmonary ventilation vary less so that after prolonged staying at an altitude of 4 to 5 km. the pulse rate and the minute volume of the heart may return almost to normal. The variations in the blood chemistry produced by the greater pulmonary ventilation also decrease.

The possibilities for human acclimatization to high altitudes are so considerable that in the Andes (South America) there are villages at altitudes of about 5 km.; the population there does hard muscular work in mines 5 to 5.3 km. above sea level. In an attempt to reach the highest point of the earth's surface (8,882 m. above sea level) Mount Chomo-lungma (Everest) on the Chinese-Nepal border several highly trained mountain-climbers managed to ascend to 8,500 m. (the summit was reached in 1953 with oxygen masks). It is possible to ascend to such altitudes (especially while doing hard muscular work) only when the body is acclimatized to these altitudes.

The increase in the number of erythrocytes and in the amount of haemoglobin, and the increase in the minute volume of the heart and in pulmonary ventilation cannot be the only factors ensuring the adaptability of the organism to oxygen deficiency. It has been shown, for example, that bleeding which leads to a 30 to 40 per cent decrease in the amount of haemoglobin is not accompanied by a lowering of resistance to hypoxia in dogs (in brief experiments) (Konradi and Filatova). No changes in the properties of the blood likely to explain the enormous ability to endure oxygen deficiency have been found in animals capable of tolerating considerable hypoxia (mammals frequently swimming for very many minutes under water—whales, cachalots). Here we probably have changes in the distribution of the blood, constriction of the vessels in a number of organs and a greater supply of blood to the brain and the heart. In addition to this, however, we must postulate a tissue acclimatization to hypoxia.

Resistance to hypoxia considerably increases in the tissues if they are repeatedly subjected to it, for example, by anaemization of the extremities through application of tourniquet (our data, Fig. 95) or by repeated injections of nonlethal doses of potassium cyanide which depresses the processes of tissue oxidation (Ginetsinsky).

Tissues repeatedly subjected to hypoxia gradually react less and less to it. This is connected with the fact that the nervous tissue (especially the cerebral cortex) whose changes are the first to determine the development of the grave consequences of hypoxia gradually become less sensitive to oxygen deficiency. The interoceptors (particularly the chemoreceptors) in all tissues probably react less to the products of incomplete oxidation which appear in hypoxia. This is why in frequently recurring hypoxia the stimulation from the interoceptors of the tissues subjected to repeated oxygen hunger changes, the cerebral cortex also reacts differently to these impulses and, it must be supposed that, in connection with this, the nervous regulation of the tissue metabolism is likewise modified.

"Hypoxic conditioned reflexes" develop to the action of all stimuli connected in time with the development of hypoxia; in recurring hypoxia all changes in the organism (changes in respiration, emptying of the blood depots, acceleration of circulation, etc.) occur faster due to these reflexes.

Factors Affecting Body Response to Oxygen Deficiency

The human and animal organisms react to oxygen deficiency differently under various conditions (even if they are similarly acclimatized).

Newborn animals and animals in the first days of their life are capable of enduring degrees of hypoxia which would prove fatal to adults.

The reason for it is that in very young animals the cerebral cortex, the organ most sensitive to hypoxia, is as yet undeveloped and cannot very greatly influence all the functions of the organism. This is confirmed by the fact that with paralysis of the cortical functions (as a result of anaesthesia or after removal of the cerebral hemispheres) animals (mice, pigeons) can be "flown" to higher "altitudes" in the pressure chamber in which the air is rarefied (Filatova).

The differences in the reaction of the cerebral cortex also explain, for example, why the animals formerly acclimatized to conditions of low temperature have a lower altitude tolerance than the animals who had lived in high temperatures; the latter die of hypoxia only upon reaching higher "altitudes" in the pressure chamber than the former (Slonim). Lower altitude tolerance in high protein diet and in radiation with ultraviolet rays is also conditioned by the changes in the state of the higher divisions of the brain. These experimental data find confirmation in practice. Thus, "mountain sickness" develops earlier on clear than on cloudy days. In southern countries it develops at higher altitudes than in northern countries (influence of the temperature factor).

All the symptoms and consequences of hypoxia appear as a result of insufficient oxygen tension in the blood and in the tissues. The loss of carbon dioxide and the alkalization of the blood connected with it, conditioned by an increased ventilation of the lungs (hyperventilation), also aggravate the condition of the body, but these disturbances are secondary and result from the reaction of the respiratory centre to hypoxia. Addition of oxygen to the inspired air eliminates all the symptoms of hypoxia (if the latter has not caused irreversible changes). With inspiration of oxygen those who lost consciousness regain it; Cheyne-Stokes respiration is replaced by normal, and normal cardiac function is restored.

There is an altitude above which one cannot rise even with an oxygen mask if one does not have a pressurized suit or cabin which protects against the effect of low pressure. The fact is that the pressure of the air entering the lungs must not greatly exceed the pressure exerted on the surface of the body or death from burst pulmonary tissue will quickly ensue. Oxygen is, therefore, inspired at a pressure corresponding to the altitude (or exceeding it by 10 to 20 or 30 mm. Hg at most). At an altitude of 10 km. this pressure equals approximately 200 mm. Hg, at an altitude of 12 km. it is 160 mm. Hg and at an altitude of 15 km. it corresponds to 80 mm. Hg.

The alveoli always contain water vapours whose pressure is 47 mm. Hg, if the air is saturated with them, and carbon dioxide with a partial pressure of no less than 20 mm. in the alveoli even after hyperventilation. Hence, the tension of carbon dioxide and water vapours in the alveoli can never be below 60 to 70 mm. Hg.

Since life is impossible when the partial pressure of oxygen in the alveoli falls below 40 to 50 mm. Hg the partial pressure of the oxygen in the *inspired* air must not be below 90 to 110 mm. This is the atmospheric pressure at the altitude of 14 to 14.5 km. and this altitude, therefore, is the limit to which a well trained flier may climb by inspiring oxygen without being isolated from the atmosphere by a pressurized suit or cabin.

Though all the symptoms of hypoxia are undoubtedly conditioned by oxygen deficiency the increase of the pH of the blood resulting from hyperventilation, which characterizes the reaction of the body unacclimatized to high altitudes, is also of some importance. In order to raise the resistance to hypoxia attempts were made to reduce the alkalosis which develops in hypoxia by including in the food acid-ash substances capable of replacing the carbon dioxide eliminated during the hyperventilation. From 5 to 10 gr. of ammonium chloride per day was administered for this purpose. The cation of ammonium chloride passes into the urea so that the hydrochloric acid formed from the NH_4Cl remains in the blood. Several investigators have noted that with this (but still better by adding carbon dioxide to the inspired air) it is possible to ascend to high altitudes without grave symptoms of hypoxia.

Effect of High Atmospheric Pressure and Oxygen Concentration on the Body

Effect of high atmospheric pressure on the body. While low atmospheric pressure leads to chemical changes conditioned by oxygen deficiency in the organism, high atmospheric pressure, which man encounters, for example, in deep-sea diving (work in caissons) acts primarily as a physical agent.

Each 10 m. of submersion increases the pressure acting on the body by one atmosphere so that at a depth of 90 m. man finds himself under a pressure of 10 atmospheres. Though this pressure is not of itself dangerous (if it does not last more than two hours) a rise from this depth without necessary precautions may lead to death.

When man is subjected to a pressure of, say, 5 atmospheres (6 kg. per 1 cm.^{2}) he can breathe air only at the same pressure. Solution of gases in a liquid is directly proportional to their partial pressures and whereas 1 ml. of blood dissolves 0.011 ml. of nitrogen during respiration at sea level at a pressure of 5 atmospheres 1 ml. of blood will dissolve 5 times as much nitrogen (nitrogen also dissolves in all tissues, especially in fatty tissue and in nervous tissue abounding in fat). During a rapid transition from a pressure of 5 atmospheres to the usual pressure the nitrogen, which passes in considerable quantities from the solution into a gaseous state, cannot reach the lungs fast enough and forms gas bubbles in the tissues and in the blood. A bubble of nitrogen in the blood may occlude the coronary or the cerebral arteries and cause instant death. Small nitrogen bubbles liberated in the nervous tissue produce severe pain.

These complications can be avoided only by a slow rise to the surface during which the nitrogen liberated from the solution has time to pass into the pulmonary alveoli. Special instructions on the speed of rising conforming to the depth and the time spent at a given depth have been elaborated.

These rules concerning the speed of *decompression* (i.e., speed of transition to normal pressure), enforced by law, guarantee against serious disorders dangerous to life. If pain appears in the joints and muscles ("caisson disease") the patient is again immediately subjected to a higher pressure which dissolves the small nitrogen bubbles in the tissues and the pain disappears at once. After this decompression is administered extremely slowly.

An acute earache due to blocking of the Eustachian tubes is a very unpleasant consequence of a transition to regions of higher pressure though it is not dangerous to life. In this case the pressure on both sides of the tympanic membrane is unequal, the membrane is pressed inward and may break.

Effect of considerable concentrations of oxygen on the organism. Oxygen, the most indispensable substance to life, is a poison which in large concentrations is destructive to the cells. A 50 per cent oxygen concentration in the air produces no ill aftereffects, but inhalation of pure oxygen at normal atmospheric pressure for more than 24 hours affects the lungs (pneumonia). Inhalation of oxygen under a pressure of 1.5 to 2.5 atmospheres provokes pathological phenomena within several hours. Since air contains a little more than one-fifth oxygen, staying under an air pressure of 7 or more atmospheres for over 4 hours is not to be allowed. If pure oxygen is inspired under a pressure above 3 atmospheres the animal dies in acute convulsions even before the lungs are affected by disease.

PART V

DIGESTION

CHAPTER 24

CHARACTERISTICS OF DIGESTION AND FOODS

Significance of Digestion and Phylogenesis of the Digestive System

A living system requires constant replenishment of the energy-giving and building materials for work, for maintenance of heat and for repair of the continuously disintegrating cells of various tissues (for example the epithelium of the skin and internal cavities, the hair, the nails, etc.).

Man and the animals get the materials for these purposes from their environment in the form of animal or vegetable food and water.

In his speech on the importance of studying the physiology of digestion I. Pavlov said: "It is not without reason that the concern for the daily bread prevails over all other phenomena of human life. It is the oldest bond which connects all living creatures, including man, with the rest of nature. The food taken in by the organism, where it changes, breaks up, enters into new combinations and breaks up again, personifies the vital process in toto, from the most elementary physical properties of the organism, such as the law of gravity, inertia, etc., to the highest manifestations of human nature."*

The process of digestion, which takes place in the alimentary canal through chemical and physical changes of the substances consumed, renders these substances absorbable and subsequently assimilable. As a result of these changes the complex and, for the most part, insoluble food substances are transformed into simpler, soluble compounds, which enter the blood, are carried by it throughout the body and are absorbed by the cells.

Nutritive substances introduced into the organism of the higher animals, other than by mouth (for example directly into the blood), are, as a rule, not assimilated by the cells; the organism treats them as foreign bodies. But artificially processed nutritive substances may in some cases be utilized in the organism when introduced directly into the blood.

Unicellular organisms, which maintain contact with the environment by their entire surface, take in the nutritive substances from this environment and digest them in their protoplasm (***intracellular digestion***). The particles of the nutritive material are drawn by the pseudopodia from the environment directly into the cell where the process of dissolution of the particles in the digestive vacuole can be observed. This dissolution is of a chemical nature with the aid of enzymes found in the protoplasma of all Protozoa.

The ability to seize and break up the particles of nutritive substances is also retained by some cells, for example leucocytes, in animals and man.

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* I. Pavlov, *Complete Works*, Vol. II, Book 2, p. 347.

Digestion in all multicellular organisms (except the lower Coelenterata) is *extracellular*, i.e., it takes place in a cavity known as the *digestive tube.*

The foods are changed chemically with the aid of enzymes secreted into the cavity of the digestive tube. The enzymes may be divided into three groups: *proteolytic, lipolytic* and *amylolytic*. As the names themselves show, these enzymes split up either proteins, fats, or polysaccharides (other enzymes, for example oxidases and amidases, are also found in some digestive juices).

The enzymes are produced in the glandular structures of the digestive tract together with various digestive juices—*secretions*, but the enzymes of the different juices which act similarly are, nonetheless, not identical. Thus, for example, the proteolytic enzyme produced by the gastric glands differs from the proteolytic enzyme of the pancreatic juice.

In addition to being changed chemically the food is also altered mechanically in the alimentary canal. During the mechanical changes the food is ground up, moved from one section of the digestive tract to another and mixed with the digestive juices; this is followed by the excretion of the unassimilated food, the desquamated cells of the epithelium and the microorganisms.

In the process of evolution the *secretory apparatus* of the digestive glands undergoes considerable changes. In its simplest form it develops from the mucous membrane which lines the internal surface of the digestive cavity. The epithelium of the mucous membrane subsequently sinks into the wall of this cavity, becomes differentiated and forms either a tube or an alveolus—the simplest secretory apparatus. At a later stage these primitive glandular apparatus are transformed in a number of places into complicated structures, into complexes of secreting elements in the shape of large glands. The latter arrange themselves near the digestive cavity and are connected with it by secretory ducts through which the product of glandular activity, i.e., the secretion, is poured into the digestive tube.

In the process of the phylogenetic development various glandular organs make their appearance already in molluscs and in Arthropoda; in insects they are connected with the differentiation of the anterior and middle intestines. In some insects salivary glands appear on the belly; their ducts open into the oral cavity and their secretion contains enzymes which hydrolize carbohydrates. An organ of a glandular nature with blind ducts (pancreas) is formed in the Arthropoda from the middle intestine. This organ communicates with the intestinal cavity into which the enzyme-containing digestive juice, produced by it, is secreted.

The motor function of the digestive apparatus is also changed in the process of evolution.

At the lower stages of development, for example, in the hydra, the digestive cavity has only one opening through which the food is taken in and the undigested remains are excreted. Already in worms the digestive cavity acquires the nature of a tube (intestine) running through the entire length of the animal's body. There are openings in the beginning and at the end of the canal—the oral and the anal. All parts of the intestine at this stage of development have the same, as yet undifferentiated, function.

In the higher animals the original canal becomes more complicated depending on the nature of their nourishment and their biological peculiarities. The anterior part of the intestine becomes differentiated forming an oral orifice and the adjacent salivary glands, gullet and oesophagus (in some animals these structures expand in the shape of a craw or a muscular stomach); the middle portion of the intestine forms the stomach, the duodenum, as well as the small intestine, the pancreas and the liver.

Methods Used in the Study of the Digestive Apparatus

The methods of studying the activity of the digestive glands and the motor function of the gastrointestinal tract were modified and developed by a number of investigators; the works of I. Pavlov have made them so perfect that on their basis the activity of the digestive glands was studied in some respects better than many other functions of the body.

I. Pavlov set himself the aim of investigating the *normal* work of the digestive glands in a healthy organism. This required the ability to collect at any time an absolutely pure secretion of the digestive glands, i.e., to solve the problem, which physiologists and physicians unsuccessfully tackled as early as the 18th century. The difficulty was precisely in obtaining the pure secretion of a perfectly healthy animal. It would seem, for example, that to obtain such a secretion as saliva, it was enough to chew some food and then to examine the saliva collected in the oral cavity. But, firstly, it is impossible to obtain a pure secretion without an admixture of food and, secondly, in this way it is possible to secure only mixed saliva secreted by the three pairs of large salivary glands, as well as by a mass of small ones dispersed in the mucosa of the mouth.

It was about as difficult to obtain gastric juice. Thus, Réaumur made his subjects swallow pieces of sponge tied to a string, which, while in the stomach, were saturated with its contents and were later extricated. It was, certainly, impossible to get pure juice in any appreciable quantities; moreover, this juice was the product of the activity of numerous dissimilar glands of a vast secreting surface. Observing the activity of individual glands under such experimental conditions was out of question.

The attempts to graft glass and metal tubes into the ducts of the glands, begun as early as the 18th century by Reinier de Graaf and later continued by Ludwig and Claude Bernard, failed to yield any positive results, because the inserted tubes soon fell out or the animal died from infection. It was thought possible to secure the juices from glands in an acute experiment, under vivisection, and watch the secretion of the juice from any gland. But disappointment awaited the investigator also in this case, since under vivisection the interference with the integrity of the organs and tissues, as well as the intoxication by narcotics, deranged the normal function of the glands. It is, therefore, impossible to observe the *normal* course of the secretory process by this method of study.

The first idea of the normal activity of the gastric glands was given by Beaumont. For eight years this remarkable physician carefully studied a Canadian hunter who, because of an abdominal wound, had an unhealing fistula which led into the cavity of the stomach.

In 1842, V. Basov, a Moscow surgeon, proposed a method of protracted, chronic study of the work of the gastric glands on an animal by means of a metal tube inserted in the stomach with the outer opening of the tube plugged. After the wound healed the gastric juice and gastric contents were obtained through this fistular tube. In 1843, Blondlot developed an analogous method in Paris. But the operation in this simple form did not, as yet, make it possible to obtain pure gastric juice and it fell to the lot of I. Pavlov to create the method, which has played an enormous role in investigating the processes of digestion and later of many other processes.

The method, developed by I. Pavlov, consists in systematic surgical operations to make the physiological study of the activity of various internal organs possible. Such a surgical operation is performed on an animal prepared beforehand, under anaesthesia and strictly aseptic conditions. The animals operated on by Pavlov's method were indispensable objects for the study of organs inaccessible to direct observation (liver, stomach, pancreas, kidney, etc.).

The operation artificially established communication of the cavity of a division of the digestive tract with the external environment or brought the duct of some gland, etc., to the exterior. This artificially created communication of the organ (stomach, intestines, gallbladder, etc.) or duct (bile, salivary, etc.) with the external environment is often designated as a *fistula* of the respective organ or duct. The operation, which prepares the animal for the experiments, is so performed as not to impair the functions of the organ studied and to retain its normal relationship with the other organs. The animal with chronic fistulas serves a long time for the study of some particular function and is frequently healthy till the end of its life. This method of experimenting is known as the *method of chronic experiments* in contrast with the vivisectional, or acute, method.

The operations performed on animals by Pavlov's method furnished the principal information on the course of the digestive process in the different parts of the digestive tract and on the composition of the digestive juices. The study of the processes, which take place in the digestive apparatus, revealed the interrelation of the different parts of this complex system and their dependence on the general state of the body and on the influence of the external environment. It also disclosed a surprising adaptation in the work of the glandular and motor apparatus to all kinds of stimuli from the external, as well as the internal, environment.

The data obtained in the experiments on animals have served as the basis for developing a number of methods for treating the diseases of the digestive organs and for studying them in man.

Pavlov's method of chronic experiments enables the physician and the physiologist to understand the phenomena occurring in the organism as mutually related. It is a truly synthetic investigation aimed at regarding the organism as a single whole, both in its normal and pathological states.

It is, of course, impossible to experiment on man the way we do on animals. But in the world of pathologic phenomena we often encounter experiments conducted, as it were, by nature and we have been able, in connection with this, to observe many very interesting aspects of digestion in the clinic. Enormous prospects thus offer themselves to the investigator for the study of the digestive processes in man.

Composition of Foods

Man consumes both animal and vegetable foods. The food substances are a source of chemical energy which is transformed into other forms of energy in the body.

In addition to their energy value the foods must also be evaluated in the light of their composition, since, besides giving energy, they serve as tissue builders. Each *foodstuff* (meat, bread, milk, etc.) is composed of *nutritive substances*, mainly of proteins, fats and carbohydrates and, hence, the foods are classified as protein, fat and carbohydrate foods. The content of proteins, fats and carbohydrates and their caloric values in the different foodstuffs are shown on page 367.

In addition to the nutritive materials each foodstuff also contains water and inorganic substances, salts, which form part of the protoplasm of all cellular structures. The various ions, absorbed along with the inorganic constituents of food, are necessary for the function of all organs and tissues. Mention should also be made of the microelements, negligible quantities of which are contained in the foods.

If we calculate the sum of alkaline equivalents ($K^{\cdot}$, $Na^{\cdot}$, $Ca^{\cdot\cdot}$, $Mg^{\cdot\cdot}$) and acid (Cl', SO_4'', PO_4''') for various foodstuffs and then add them up (designating the surplus of alkaline equivalents by a plus and that of the acid equivalents by a minus) we will be able to classify the foods (Table 8) as acid and alkaline foods. All meat, fish and (in a lesser measure) grain products, including bread, belong to acid foods (because of the excess of the Cl', SO_4'' and PO_4''' ions over the sum of the $K^{\cdot}$, $Na^{\cdot}$ and $Ca^{\cdot\cdot}$ equivalents). Milk, different vegetables, fruits and berries belong to foods with an excess of bases. The sour taste of many fruits depends on the organic acids they contain; the latter are rapidly oxidized in the organism and are, therefore, not considered in the evaluation of the amount of acid equivalents absorbed by the body.

Table 8

Acidity and Alkalinity of Foodstuffs (in c.c. of Normal Acid or Alkaline Solution, Necessary for the Neutralization of the Surplus of Inorganic Bases or Acids per 100 gr. of Food)

(After Berg)

Foodstuffs	Sum of base equivalents	Sum of acid equivalents	Surplus of alkaline (+) or acid (–) equivalents
Blood	16.76	11.33	+5.43
Beef	26.40	33.66	-7.26
Veal	13.14	36.10	22.96
Pork	15.35	27.82	12.47
Pike	19.85	22.60	-2.75
Herring	534.43	551.78	-17.35
Caviar	57.71	69.32	-11.61
Egg white	14.20	22.47	-8.27
Woman's milk	7.04	4.79	+2.25
Cow's milk	13.08	11.39	+1.69
Butter	15.64	19.97	4.33
Bread	15.79	26.78	10.99
Potatoes	13.85	7.95	+5.90
Lettuce	21.30	7.18	+14.12
Tomatoes	20.72	7.05	+13.67
Cucumbers	70.08	38.58	+31.50
Apples	2.21	1.37	+0.84
Oranges	12.46	2.85	+9.61

Most of the nutritive substances are colloids in their physicochemical properties. In colloids the number of particles in a definite volume may vary with different conditions. Thus, the ratio of the total surface of the particles to their mass, i.e., the degree of dispersion, also changes. This is important because the enzymes act on the surface of the particles. The greater the dispersion, the better the conditions for the digestion of the given food in the alimentary canal.

Lastly, we must mention one more property of foodstuffs, the so-called *bulkage* they contain, the substances which are not assimilated by the organism. Cellulose, which is not digested or assimilated in the alimentary canal of the carnivores and man, is one of these. These substances, however, may greatly increase the mass of food taken in, which is important in that it produces the feeling of satiety. The bulkage substances, which form part of the semiliquid food mass (chyme), at the same time influence the stimulation of both the secretory and motor functions of the digestive apparatus (especially, the intestines).

CHAPTER 25

DIGESTION IN THE ORAL CAVITY

In the higher animals and in man the digestion of nutritive substances begins in the oral cavity. Retained in the mouth but a short time (15 to 20 seconds), the food is masticated (ground into small particles), moistened with saliva and transformed into a bolus. Chemical digestion of certain constituents of the food begins in the mouth, owing to the action of the saliva.

Composition of Saliva

The saliva of man and many animals is a mixed secretion of three pairs of large salivary glands—the parotid (*gl. parotis*), the submaxillary (*gl. submaxillaris*) and the sublingual (*gl. sublingualis*), as well as of a mass of small glandules scattered in the mucosa of the mouth.

The mixture of the secretions of all these glands is a colourless, viscid liquid, which contains 98.5 to 99 per cent water and 1 to 1.5 per cent of a dense residue (of salts and organic substances). The reaction of saliva is mildly alkaline ($pH = 7.4$ to 8.0); the saliva in children during the first years of their life is more acid than in adults.

Saliva is always slightly turbid due to fine particles of epithelium of the buccal mucosa, leucocytes, etc. (so-called salivary corpuscles); it frequently contains food remains together with microorganisms. Due to the volatilization of the carbon dioxide from the saliva, some time after it has been collected in a test tube, a calcium carbonate is precipitated making the saliva cloudy.

The dense residue, obtained after the evaporation of the saliva, consists of organic and inorganic substances. The organic substances are represented mainly by proteins; the saliva secreted by the submaxillary and the sublingual glands contains, among the proteins, gluco-proteid-mucin which makes it viscid.

Of the inorganic constituents the saliva contains chlorides, sulphates, carbonates of sodium, potassium, calcium and magnesium and traces of ammonia. The saliva of man and some animals also contains potassium sulphocyanate (about 0.01 per cent). Certain metabolites (CO_2, carbonic acid salts, urea, etc.), as well as drugs introduced into the organism (e.g. iodine) are discovered in the saliva.

The saliva of man and some animals (ape, certain herbivores, bear) contains an enzyme called *ptyalin* which converts the polysaccharides into disaccharides, particularly, maltose, the latter being further converted to glucose by another enzyme called *maltase.*

Ptyalin acts best only under definite environmental conditions, namely, at a temperature of 37 to 40° C and in a mildly alkaline medium; at 0° C and in an acid medium the action of the enzyme ceases. Starch is converted by the ptyalin in the oral cavity but for a short time, since the bolus quickly enters the stomach. There the action of the ptyalin continues until the acid gastric juice saturates the food mass, lying in layers, and renders the further conversion of starch impossible. The salivary enzymes continue to act in the stomach for 20 to 30 minutes with the gastric juice beginning to act only after the alkaline reaction has changed to an acid reaction.

Structure of Salivary Glands

The salivary glands are divided into: a) *serous* glands, secreting saliva which contains a good deal of protein, but no mucus and, therefore, no mucin (parotid glands in man); b) *mucous* glands, secreting saliva with a large content of mucin, i.e., mucous substance (sublingual glands in man); c) *mixed* glands, secreting saliva with an admixture of mucous substances (submaxillary glands in man).

When not secreting, the cells of the salivary glands are larger and spherically shaped; the nuclei of the cells are pale and are located at the basal part of the cell; this basal part adjoins the basement membrane. The cells are filled with secretory granules, except a narrow strip near the nucleus. The nucleus is, undoubtedly, also involved in the secretion. The gland is divided into lobules. The lumen of each lobule of the gland is narrow because it is surrounded by cells filled with secretory material. This applies in equal measure to the serous and the mucous glands.

During the secretion the granules gradually disappear, separate small granules merging into larger ones, which move out into the lumen of the lobule. At this time the threads of protoplasm in the glandular cells become clearer and it appears as though streamlets of liquid flow through the cells. But the secretion is accumulated in the gland not only when it is in a state of rest, but also during its secretory activity. After protracted secretion ceases the structure peculiar to the gland at rest is gradually restored. Its cells resume their spherical shape and the nucleus is forced down towards the base of the cell. When the gland rests the secretion accumulates unevenly: while some of the cells are already filled with granules, the others still have very few of them.

Like all the other organs of the digestive system the salivary glands also have aggregations of nerve cells (ganglia) in their tissues or over their entire surface; the ganglia receive nerve conductors, secretory nerves, from the central nervous system. The nerve trunks, which reach the glands, also have other types of nerve fibres—vasomotor and afferent; the latter carry the impulses from the glands to the central nervous system.

Vascular and lymphatic capillaries closely adjoin the basement membrane of the glands. During the secretory activity of the glands the vessels become considerably dilated, blood is supplied in greater quantities and lymphatic circulation is, probably, increased. The ducts of the salivary glands serve for the emptying of the secretion produced in the glandular cells. At the same time the secretion of the mucous cells, located in the walls of the duct, is mixed with the secretion of the gland. There are many elastic and muscle fibres in the walls and terminal parts of the gland ducts. The contractile (muscle) elements force out the accumulated secretion.

It is possible that the first nervous impulse, which runs along the secretory nerves, creates a difference in osmotic pressure between the protoplasm of the gland cells, on the one hand, and the tissue liquid and blood, which surround them, on the other. This moment is, apparently, signalled to the nerve centres and results in the creation of a closed circuit of nerve impulses, which flow from the periphery to the centre and back again. It is in this manner, apparently, that the uninterrupted course of the secretory process is ensured until a definite limit of efficiency, primarily of the nerve cells of the central nervous system, is reached.

There are also other hypotheses of the way secretions are produced and secreted.

Methods of Studying the Activity of Salivary Glands

To study the secretory activity of the salivary glands and to obtain a pure secretion from each gland separately Pavlov developed a method of producing chronic fistulas in the ducts of the salivary glands. This method made it possible to study in detail, both quantitatively and qualitatively, the secretory function of each gland according to the various stimuli which act on the animal under natural conditions.

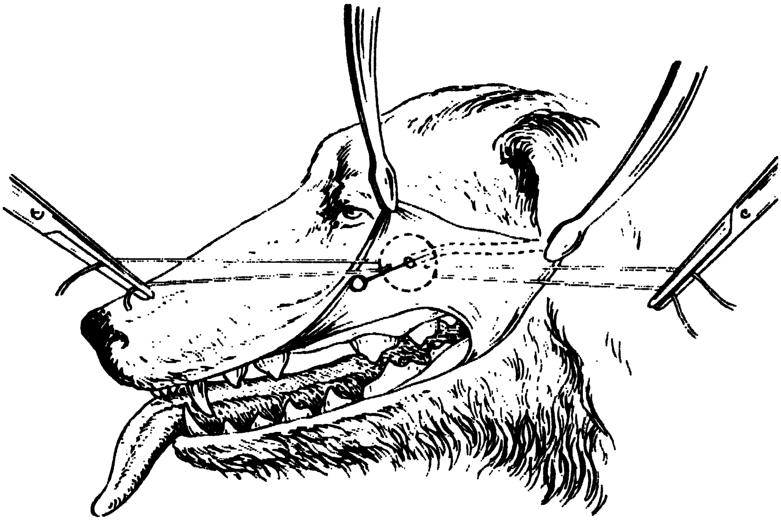

Fig. 96. First step in creating chronic fistula in duct of the parotid gland. Probe is in the duct and the stay sutures are on. Part of duct to be dissected is shown by dotted line (after N. Podkopayev).

The operation for producing a fistula in the dog's salivary duct is performed as follows. A piece of the mucous membrane of the mouth, where the opening of the duct of the parotid or the submaxillary gland is located, is excised (Fig. 96). The duct and the piece of mucosa are separated from the surrounding tissues and are brought to the outside through a puncture in the cheek or in the floor of the oral cavity (Fig. 97). The piece of mucosa, brought to the exterior, is sewed to the skin. The wound in the oral cavity is closed. After a while the piece of mucosa grows into the skin of the cheek or chin. Following this a funnel is placed against the opening of the duct and the saliva can be collected into small cylinders, attached to the funnel (Fig. 98), separately from the parotid, as well as from the submaxillary and the sublingual glands (the ducts of the two last glands merge, forming a common opening).

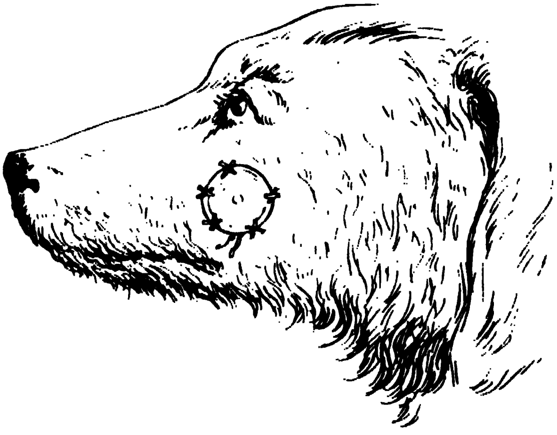

Fig. 97. Second step in producing chronic fistula in duct of the parotid gland.

Separated disk of mucosa has been brought to exterior through incision in cheek (after N. Podkopayev)

Excluding one or two of the six large salivary glands from the normal digestion in the oral cavity in no way affects it. It is possible to observe the activity of the salivary glands in an animal with the duct brought out on to the cheek or chin under perfectly normal physiological conditions. The method of a chronic fistula in the salivary gland developed on dogs has been successfully used on a number of other animals, including cats, mice, goats, pigs and monkeys.

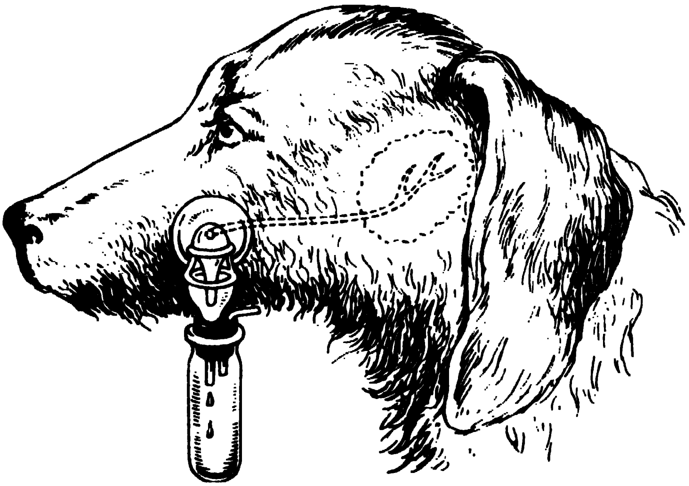

Fig. 98. Dog with fistula of the parotid gland.
Funnel and test tube for collecting saliva are fastened to cheek in region of exteriorized opening of the duct.

Stimuli of the Salivary Glands

Saliva is always secreted when foodstuffs are introduced into the oral cavity, the amount and composition of the secreted saliva varying with the physicochemical properties of the food. In the dog the amount of secreted saliva depends, primarily, on the dryness of the food. The drier the food, the more saliva is secreted. When bread, which contains about 50 per cent water, is eaten, less saliva is secreted than when powdered dry bread is consumed, in which there is hardly any water. For example, when the dog is fed 20 gr. of bread his parotid gland secretes 1.18 ml. of saliva and the submaxillary 2.9 ml.; when the same dog is fed 10 gr. of dry bread his parotid gland secretes 2.5 ml. and the submaxillary 3.8 ml. of saliva. It must, thus, be recognized that different mechanical stimulation of the oral cavity, primarily depending on the dryness of the food, is responsible for the different work of the salivary glands.

In addition to being stimulated by food the secretion of saliva is also provoked by the so-called rejected substances which may injure the mucous membrane of the oral cavity. Saliva is vigorously secreted, for example, when the mucosa of the mouth is irrigated with acid or alkaline solutions, when sand is put into the mouth, etc.

The figures in Table 9 show graphically that the amount and composition of the saliva secreted depend on the physicochemical properties of the substances introduced into the mouth.

The importance of moistening the food with saliva is, therefore, obvious; it aids in the formation of a bolus easy to swallow. If no saliva is secreted very dry food cannot be swallowed. The composition of the saliva secreted on the food and on rejected substances differs. The saliva secreted on foodstuffs is rich in organic constituents, whereas the saliva secreted on rejected substances is poor in dense substances. When acid is introduced, however, the parotid gland secretes saliva rich in protein, which, probably, participates in the neutralization of the acid (Table 9).

The composition of the saliva also depends on the rate of its secretion. If the saliva is secreted (on foodstuffs) fast and abundantly, it is richer in the dense residue than when it is secreted scantily. But if the saliva is secreted abundantly and over a long time, it becomes gradually poorer in organic substances. After protracted secretion the cells of the salivary glands are poor in granules.

We see that the amount and composition of the saliva secreted depend in large measure on the nature of the stimulation which causes the secretion. They also depend on the general state of the body. For example, if we feed dogs carbohydrate food, the usually absent ptyalin will appear in their saliva (Razenkov). If a dog is not given liquid for a long time, water becomes a vigorous stimulant of salivary secretion (Fursikov).

Table 9

Amount and Composition of Saliva Secreted per Minute by the Mixed (Submaxillary and Sublingual Together) and Parotid Glands of the Dog When Fed and When Rejected Substances Are Placed in the Mouth

(Average figures by Zelgeim from Pavlov's laboratory)

					Parotid Gland			
Kind of Substance	saliva per minute (in ml.)	dense substances (in %)	organic substances (in %)	ash (in %)	saliva per minute (in ml.)	dense substances (in %)	organic substances (in %)	ash (in %)
Meat	1.1	1.27	0.96	0.32	1.4	0.93	—	—
Meat powder	4.4	1.48	0.87	0.61	1.9	1.46	1.1	0.36
Milk	2.4	1.41	0.90	0.42	0.7	0.71	—	—
White bread	2.2	0.97	0.59	0.38	1.6	1.18	0.78	0.40
Dry bread	3.0	1.43	0.97	0.46	1.9	1.46	1.10	0.36
Sand	2.0	0.65	0.27	0.33	1.3	0.57	0.10	0.47
0.5% HCl	4.3	0.78	0.18	0.50	2.0	1.20	0.77	0.43
2% solution of acetic acid	5.4	1.05	0.39	0.66	4.5	1.17	0.57	0.60
0.25% solution of caustic soda	5.8	0.90	0.30	0.60	5.0	0.86	0.22	0.64

The work of human salivary glands has been repeatedly observed under clinical conditions in patients in whom fistulas were formed by an injury. But the salivary secretion in man has been particularly fully studied since N. Krasnogorsky had proposed special capsules (Fig. 99) which are placed on the mucosa of the mouth against the opening of the duct of the salivary gland. (Similar capsules were proposed by Lashley.)

The capsule consists of two chambers—an inner chamber and an outer one that surrounds it. The inner chamber serves to collect the saliva which is then removed from the oral cavity by a rubber tube; this tube is, in its turn, placed over a metal tube which communicates with the inner chamber. The outer chamber serves to fasten the capsule on the buccal mucosa by suction. The capsule holds fast in the mouth and permits of free chewing and swallowing of food (Fig. 99).

The study of salivary secretion has shown that in animals it is governed by other laws than in man. In human saliva no such differences in the amount of the dense residue are observed when various stimulants (food and rejected substances) are placed in the mouth as there are in that of dogs (Biryukov). Besides, while water causes no salivary secretion in dogs it is quite a strong stimulant of salivary secretion in man. In the absence of stimulants, which cause salivary secretion, the salivary glands of dogs are at rest, whereas in man constant secretion of the salivary glands is observed even when there is no stimulation at all (0.1 to 0.2 ml. per minute); salivary secretion is sharply increased when stimulated by food.

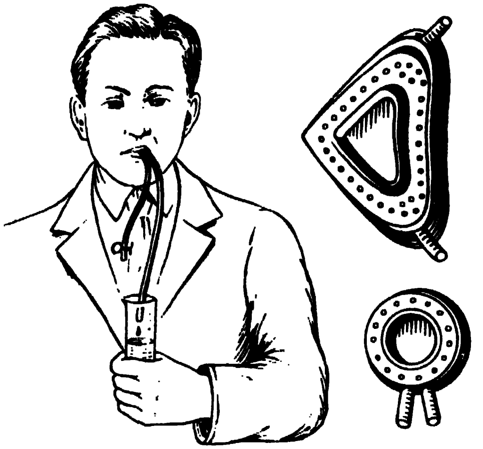

Fig. 99. Right—Krasnogorsky's capsules for collecting human saliva: below—from the parotid gland, above—from the submaxillary. Left—collecting human saliva with Krasnogorsky's capsule.

The saliva secreted by the small glands in the oral cavity keeps the membranes of this cavity moist. When the mucous membrane of the oral cavity dries (for example, in speech) a certain amount of saliva is secreted mainly by the small glands, scattered throughout the mucosa. Like any other weak mechanical stimulation of the oral cavity, chewing causes only insignificant salivary secretion. It must be mentioned, however, that longer chewing of the bolus prepares it better for further digestion.

Innervation of Salivary Glands

We see how regularly the salivary glands begin to secrete in response to a stimulus in the oral cavity. The mere fact that secretion of saliva begins a short time (fraction of a second) after the action of the stimulus shows we are dealing with a reflex, i.e., with such an activity of the organ which takes place because of the transfer of the impulse to it over the reflex arc from the receptor through the central nervous system.

We shall now consider the *reflex arc of the salivary secretion reflex*. Large numbers of receptors whose stimulation always causes salivary secretion (the receptor field of this reflex) are located in the oral cavity, especially on the surface of the tongue, where there are special taste buds, which react to the action of bitter, salty, sour and sweet substances (Chapter 68). The different sections of the mucous membrane of the mouth do not equally react to the various stimuli. The most excitable parts of the tongue are its base and, to a lesser degree, its tip and inferior surface. Thermal stimuli are responded to by nearly the entire surface of the mucosa of the mouth, while the root and tip of the tongue, the hard and soft palates and the upper lip react quite strongly to mechanical stimuli. The afferent fibres from the receptors in the oral cavity run to the central nervous system in the lingual branch (*n. lingualis*) of the trigeminal nerve, in the glossopharyngeal nerve (*n. glosso-pharyngeus*) and in the superior laryngeal branch (*n. laryngeus superior*) of the vagus.

There are two methods in physiology to determine the significance of each nerve trunk in innervational regulation: observation of the consequences of *cutting* a nerve and observation of the results of ***stimulation*** of its severed ends. Tests of the above-mentioned nerve trunks by these methods have shown they are really afferent conductors of impulses, which arise when the receptors in the oral cavity are stimulated. Artificial stimulation of the *proximal* segment of the lingual, glossopharyngeal and superior laryngeal nerves is followed by considerable secretion of saliva, but after all the afferent conductors of the oral cavity, the nose and the pharynx are cut, the stimuli, which act on the mucous membrane of the oral cavity, cause no more salivary secretion.

A number of receptors in the oral cavity is stimulated in the act of eating. By registering bio-currents from the lingual branch of the trigeminal nerve one can observe that application of different stimuli to the tongue gives rise to impulses connected with the mechanical, thermal and chemical stimulation of the receptors of the oral cavity. These impulses have different frequencies and are differently distributed in time; for example, the impulses from a mechanical stimulation of the tongue arise in the fibres of the lingual nerve over lesser intervals of time after application of the stimulus than the impulses following a chemical stimulus (data of laboratory headed by P. Anokhin).

Stimulation of the afferent conductors, not related to the oral cavity, for example, the sciatic nerve, may under certain conditions also cause secretion of saliva. This is due to the fact that salivary secretion in animals is not only of digestive significance; for example, secretion of saliva in dogs plays an important part in the regulation of heat in the body; it is also secreted when the dog licks his wounds, when the secretion of saliva plays the part of a protective reaction because it contains bactericidal substances.

The afferent fibres running from the receptors of the oral cavity in the trunks of the lingual, glossopharyngeal and superior laryngeal nerves enter the medulla oblongata. In the medulla the afferent fibres come in contact (probably through synaptic neurons) with the nerve cells which give off efferent fibres to the salivary gland. The efferent fibres for the submaxillary and the sublingual glands run in the *chordae tympani*. This nerve arises from the nuclei (of aggregations of cells) of the VII pair of cranial nerves in the medulla oblongata. Leaving the brain the nerve fibres enter *canalis facialis* and further along the tympanic cavity. Coming out of the tympanic cavity they join the lingual nerve (branch of the V pair).

The parotid gland receives nerve fibres from the nuclei of the IX pair of cranial nerves. These fibres run through the tympanic cavity as part of the so-called Jacobson's nerve (*n. Jacobsoni*), then enter the *gangl. oticum*, and emerging from it in thin branches they approach the gland under the name of the *auriculo-temporal* nerve.

Having traversed the complicated path described above, the efferent preganglionic parasympathetic nerve fibres of the salivary glands end in ganglionic cells. These nerve cells of the parasympathetic ganglia are located both in the tissue of the gland and near it, for example, in the *sublingual ganglion*. *Postganglionic* fibres run from the cells of these ganglia and enter the tissue of the gland as several branches. The fibres of the vegetative nervous system just described belong to its *parasympathetic* division.

In addition to parasympathetic fibres the salivary glands are also innervated by *sympathetic* fibres. The preganglionic sympathetic fibres innervating the salivary glands upon leaving the spinal cord run to the cervical sympathetic nerves of the superior cervical ganglion which gives rise to postganglionic fibres travelling along blood vessels to all three large salivary glands.*

To study the action of the aforesaid nerves on the salivary glands the nerves are stimulated in an acute or chronic experiment. In an acute experiment the nerves of the gland are separated and cut in order to apply stimulating electrodes to their peripheral ends. To observe the secretion of the saliva a glass canula is inserted into the duct of one or several glands so that the saliva flows out through the canula. An abundant secretion of *watery* saliva is observed within 2 to 5 seconds after stimulation of the *chordae tympani* with induction current. The secretion of saliva continues for some time after the stimulation has ended.

The effect of stimulating the *chordae tympani* is so strong that with a rhythmic action of the stimulus it is possible to obtain up to 200 ml. of saliva from the gland, whereas the gland itself weighs 7 gr. Longer stimulation of the cranial nerve increases the secretion of saliva, but the organic substances in the secretion gradually diminish. The amount of mineral salts increases to a certain extent as the stimulation is intensified.

Cutting the parasympathetic fibres which run to the salivary gland (i.e., cutting the corresponding cranial nerve) renders reflex secretion of saliva impossible. But 24 hours after the *chordae tympani* are severed the salivary gland begins to secrete saliva and secretes it incessantly for a period of 20 to 60 days. C. Bernard termed this secretion of the denervated gland paralytic. Its mechanism is not clear; the secretion is seemingly connected with some change in the excitatory apparatus which occurs after the specific nerve is excluded. According to Walter B. Cannon, this phenomenon is connected with the increased sensitivity of the denervated glands to chemical stimuli.

Stimulation of the peripheral end of the cervical *sympathetic* nerve, which runs to the submaxillary gland, also causes secretion of saliva. The sympathetic nerve has something to do with the other salivary glands as well (with the sublingual and in most animals with the parotid). But the effect from the stimulation of the sympathetic nerve differs characteristically from that of stimulating the cranial parasympathetic nerve fibres in that 1) considerably less saliva is secreted when the sympathetic nerve is stimulated, 2) the "sympathetic" saliva is more viscous, because it contains considerably more organic substances, and 3) there is less salts in the "sympathetic" saliva than in the "parasympathetic." Under sustained stimulation of the sympathetic nerve, as under stimulation of the chordae, the saliva grows poorer in organic substances.

If we stimulate the sympathetic nerve first and then stimulate the chordae, the chordal saliva becomes richer in dense constituents. The same occurrence is observed when the parasympathetic and the sympathetic nerves are stimulated simultaneously. Stimulation of the parasympathetic nerve prior to the stimulation of the sympathetic nerve leads to an increase in secretion in response to the stimulation of the latter, and sometimes 10 times as much saliva is secreted as when the sympathetic nerve is stimulated without the preliminary influence of the parasympathetic. The interaction of the parasympathetic and the sympathetic nerves carrying to the salivary glands impulses which normally involve the higher divisions of the brain is responsible for the work of the gland which is observed in the animal under natural physiological conditions.

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* In man and in many animals, the sympathetic fibres run in the neck in a common trunk with the parasympathetic fibres of the vagus.

The centre of the unconditioned reflex of salivary secretion, i.e., the division of the central nervous system, where the excitation from the afferent leg of the reflex arc is transferred to the efferent, is the *medulla oblongata.* Its stimulation causes secretion of saliva, whereas its destruction makes reflex secretion of saliva impossible. Because of this the *centre of salivary secretion* is considered to be located in the medulla oblongata. Its participation is necessary in every reflex salivary secretion, but it is not the only central point the stimulation of which can cause secretion of saliva. Mislavsky and other investigators had already shown that secretion of saliva could also be caused by stimulating the cerebral cortex.

The reflex of salivary secretion is always produced by the action of certain stimuli on the receptors in the oral cavity. Since this reflex occurs invariably from the moment the animal is born Pavlov termed it an *unconditioned reflex.* It has long been known, however, that the salivary glands of dogs, as well as of man, begin to act not only under the influence of food in the mouth, but also at the sight and odour of food or at the sounds, which usually attend the act of eating. This observation was made long ago and the phenomenon is known as "psychic salivary secretion." The analysis of this long-known fact served for Pavlov as the point of departure in the elaboration of one of the most important problems in physiology: the problem of the mechanism of activity of the higher division of the central nervous system—the cerebral cortex.

The sight or smell of food do not act on the receptors in the oral cavity, but on other receiving apparatus—the eye and the nose. The secretion of saliva in response to stimulation of these receiving apparatus is, both quantitatively and qualitatively, an exact, though reduced, replica of the salivary secretion which occurs when food is taken into the mouth. But for the sight or smell of food to cause secretion of saliva it is necessary that the stimuli, which attend the act of eating (sight and smell of food, conditions under which food is taken) act once or several times *simultaneously* with the action of the food on the receptors in the oral cavity. The dog, who never ate meat, will not secrete a single drop of saliva upon seeing or even smelling it. But if it did eat meat once or several times its sight and odour will cause salivary secretion.

The reflex of salivary secretion in response to stimulation of the receptors in the oral cavity is inborn. Salivary secretion under the action of stimuli on other receiving surfaces is also reflex, but this reflex is not inborn, is not a reflex of the species, but is elaborated in the process of individual life. This reflex Pavlov termed a *conditioned reflex.*

Participation of the medulla oblongata in the reflex arc is enough to produce the unconditioned reflex of salivary secretion, whereas the conditioned reflexes are produced and elaborated *only with the participation of the cerebral cortex.* The inherited unconditioned reflexes can, thus, be produced by the lower divisions of the central nervous system, whereas the new relations of the organism to its environment, elaborated in the course of its life, are established by the activity of the higher divisions of the brain.

Conditioned reflexes of the salivary gland are formed, as before stated, when some indifferent agent, i.e., one which does not of itself cause salivary secretion, acts simultaneously with the stimulation of the oral cavity. Following this, the formerly indifferent agent becomes a stimulus to the salivary gland. The accessory properties of a food (odour, sight of food) inevitably become conditioned stimuli because in normal eating they always act simultaneously with the unconditioned stimuli. The conditioned reflex, which results from the action of the above-mentioned stimuli, has, therefore, been termed a *natural* conditioned reflex.

The normal secretion of saliva, when food is taken, is made up of the interweaving of conditioned and unconditioned stimuli, the action of the former always preceding the latter. Owing to the formation of conditioned reflexes the salivary glands (also other divisions of the digestive system, as we shall see later) may become active (be "mobilized") even before food is taken when acted upon by the signals connected with the forthcoming act of eating.

Neurohumoral Stimulation of the Secretion of Salivary Glands

The salivary gland may also be stimulated by the action of a stimulus brought to it by the blood (this stimulus acts, primarily, on the nerve endings in the gland). Injection of 1 to 3 mg. of the alkaloid pilocarpine into the blood causes an abundant secretion of saliva, which sometimes lasts from 1 to 2 hours. Pilocarpine acts on the neuroglandular apparatus; the blood supply to the gland is increased at the same time. The glands are also stimulated in asphyxia or in holding the breath, in ether anaesthesia and by the action of certain other poisons. In a number of cases the chemical stimuli act not only through the blood on the peripheral nervous apparatus, but also directly stimulate the central nervous structures.

Blood Supply to the Salivary Glands During Secretion of Saliva

During the activity of the salivary glands the amount of blood flowing through them sharply increases (3- to 4-fold). This increase in the blood supply is, apparently, a matter of reflex action. The chemical and mechanical changes in the gland stimulate its receptors. The impulse, which arises in the receptors of the gland, is transmitted to the central nervous system, to the vasomotor centre, whence impulses run along the vasomotor nerves to the blood vessels in the periphery and regulate their lumens. Experiments show that in addition to the secretory nerve fibres the salivary glands are reached by vasodilators (in the *chordae tympani*) and vasoconstrictors (in the sympathetic nerve).

Proper blood supply to the gland is, undoubtedly, a necessary condition for its work, which sometimes lasts very long. By stimulating the secretory nerves experimentally it is also possible to secure a secretion from a bloodless gland, but the amount of saliva will be insignificant, the excitability of the nerves under these conditions decreases and the salivary secretion soon stops.

Mechanism of Work of Secretory Cells

There were attempts to explain the mechanism of salivary secretion as a result of filtration of liquid from the blood through the cells of the salivary gland under the influence of an increased blood supply and high blood pressure. It turned out, however, that saliva was also secreted in a severed head of an animal when the secretory nerves were stimulated. Moreover, the pressure of saliva in the duct of the gland is often higher than the blood pressure in the arteries (Ludwig).

Hence, it is not the blood pressure that causes the water to pass from the plasma through the vessels and cells of the gland into the saliva. It is impossible to explain the secretion of saliva as a result of simple filtration. Normal secretion of saliva, certainly, needs a supply of blood, which brings to the gland the necessary material and water for the production of the constituents of the secretion, but, though this blood supply is necessary for sustained work of the glands, blood pressure in the vessels is not the cause of the secretion. Production of the secretion must be ascribed to the activity of the glandular epithelium itself. This activity finds its expression in the above-mentioned changes, which occur in the glandular cells (p. 241).

Assuming that the production of saliva and its *secretion* by a flow of liquid are two separate processes, Heidenhain advanced the theory of secretion in 1868, according to which the fibres of the cranial nerves (parasympathetic) cause the secretion of water and salts, while the impulses, which run through the sympathetic fibres, condition the secretion of the organic substances. The nerve fibres, which condition the secretion of water and salts and which run mainly in the cranial nerve, were termed *secretory* by Heidenhain, whereas the fibres, which condition the secretion of the organic substances and which prevail in the sympathetic nerve, were named *trophic*. The different relations between these stimulations determine the different character of salivary secretion in each particular case. The amount of salts in the saliva directly depends, according to Heidenhain, on the speed of the secretion: the increased secretion of saliva is connected with an increase in the content of inorganic constituents; the amount of these constituents decreases when the secretion slows down. Heidenhain's theory, however, does not explain all the aspects of the activity of the salivary glands and, in a number of points, finds no confirmation. There is no generally accepted theory of the mechanism of salivary secretion as yet.

The ideas of the way excitation is propagated from the nerve fibres to the effectors have considerably changed of late. According to the formerly prevailing physical point of view the transfer of the impulse from the nerve to the gland was a change in the polarization of the dividing surfaces between the nervous and the glandular apparatus. It has now been demonstrated that when the secretory nerves are stimulated a special chemical substance appears in the blood flowing from the gland and this substance stimulates the gland and causes a number of chemical transformations in the glandular cell. Stimulation of the *chordae tympani* causes the secretion not only of the submaxillary gland whose nerves are intact, but also the secretion of another gland whose nerves were preliminarily cut. These observations indicate that when the secretory nerves are stimulated special substances are produced in the gland, which are in themselves capable of causing the secretory activity if they get into another gland through the blood. Tests of this substance on different test-objects have shown that it can be likened to acetylcholine. There are also indications that along with acetylcholine another and more stable substance is produced in the gland and is secreted with the saliva. This substance dilates the blood vessels and stimulates the activity of the gastric glands.

The nerve impulses also influence the contractile elements of the gland. Contraction of these elements moves the accumulated secretion through the minutest ducts of the gland. The movement of the secretion along the secretory capillaries apparently causes the stimulation of the interoceptive nervous apparatus of the gland. This stimulation is transmitted to the centres, whence waves of excitation run to the periphery, to the glandular cells and the vasomotor apparatus. A circular process, as it were, is created and this process supports the sustained work of the gland.

Mechanical Processes in the Oral Cavity During Eating and Digestion

In addition to being chemically changed in the mouth the food is ground up and saturated with saliva; then the bolus is moved to the base of the tongue, which causes the act of deglutition as a reflex in response to the stimulation of the receptors of the soft palate by the bolus.

Sucking. When the mouth is closed the tongue completely fills the oral cavity which results in a pressure 2 to 4 mm. H_2O lower than atmospheric; the lower jaw is passively pressed against the upper by the air pressure. Since there is no communication between the oral cavity and the external air because the lower jaw drops, the tongue is drawn down and back (the drawing of the tongue back can be compared with the backward movement of the piston in the cylinder of a pump) and sucking results. At this time the pressure in the oral cavity may be lower than atmospheric by 100 to 150 mm. H_2O. When a child sucks his mother's breast milk enters into the rarefied space of the oral cavity. The tongue, lips and jaws are moved by the *genioglossi, sterno-hyoidei, sterno-thyreoidei* and other muscles. These muscles are innervated by the facial nerve, the muscles of the lower jaw—by the trigeminal and facial nerves, and the muscle fibres of the tongue—by the lingual nerve. Branches of the V pair of nerves serve as the afferent nerves which stimulate sucking.

Mastication. Mastication is an intricate complex of movements performed by the contraction of the muscles of mastication (*masseteres*, external and internal, *pterygoidei* and temporal muscles) and the muscles of the tongue and cheeks. Mastication grinds the food into small particles and aids in moistening it with saliva and forming a bolus.

During mastication man performs various movements with his lower jaw, which alternately moves horizontally and vertically. Owing to these movements the lower teeth come in contact with the upper. The front teeth bite the food off. The food is crushed by the premolars, when the lower jaw rises and the rows of teeth close, and is ground up by the molars during the horizontal displacements of the lower jaw. The food is delivered between the rows of teeth by the contractions of the muscles of the tongue and cheeks. The muscles of the lips close the oral cavity, deliver the food to the oral cavity and prevent its falling out of the mouth.

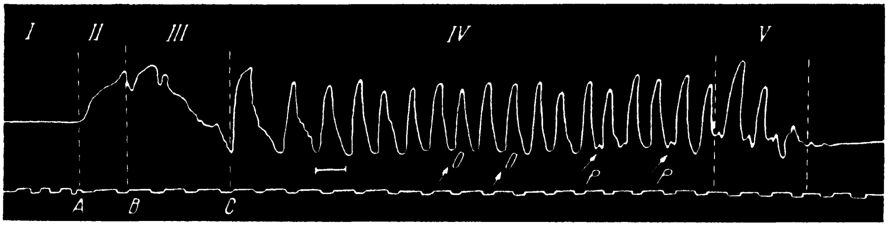

Fig. 100. Kymogram of single masticatory period in man.

I—rest phase; *II* phase of introducing food into mouth; *III*—tentative phase of mastication; *IV* main phase of mastication; *V*—phase of bolus formation and swallowing. Rise of curve *(AB)* corresponds to opening of mouth, its drop *(BC)* to closing of mouth; *O* moment teeth close and crush food; *P*—moment food is ground (after I. Rubinov).

A graphic study of the masticatory movements of the lower jaw makes it possible to establish their definite repetitiveness in the mastication of each piece of food; the repeating cycle of these movements is known as a single masticatory period. The masticatory period is made up of five phases following each other: phase 1—rest, phase 2—introduction of food into the oral cavity, phase 3—tentative masticatory phase, phase 4—basic masticatory phase, phase 5—formation of bolus and beginning of deglutition (Fig. 100). The correlation of the length of the separate phases and the nature of the masticatory movements may change according to the size of the piece of food, its hardness and the taste elements of the food; it represents considerable individual peculiarities (Fig. 101). The mechanical properties of food and, hence, the mechanical stimulation of the oral cavity are of the greatest importance to mastication.

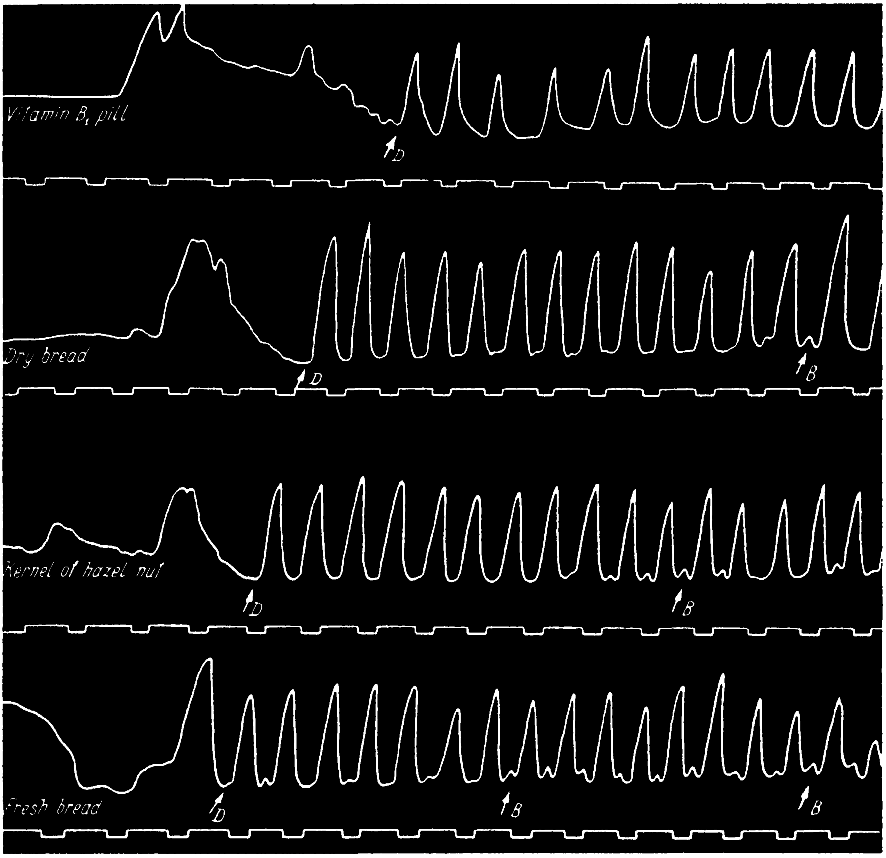

Fig. 101. Kymogram of human masticatory movements during mastication of substances of varying hardness (Vitamin B_1 pill, dry bread, kernel of hazel-nut and fresh bread).

D—beginning of food crushing; B—beginning of food grinding (after I. Rubinov).

The masticatory reflex is called forth when the mucous membrane of the oral cavity is stimulated; the impulses from the receptors run along the second and third branches of the trigeminal nerve. The reflex centre of mastication, directly subordinated to cortical influences, is located in the medulla oblongata. The efferent innervation of the muscles of mastication is also effected by branches of the trigeminal nerve.

The natural conditioned reflexes, formed all through life, are of considerable importance to the regulation of the masticatory movements. Thus, the experiments of I. Tsitovich established that dogs, grown exclusively on liquid food (milk), devoured pieces of meat but very slowly.

In man mastication of soft food, following the mastication of hard substances, calls forth a masticatory period characteristic of hard food. Formation of conditioned reflexes to masticatory movements in connection with the hardness (consistency) of food has thus been proved.

The masticatory movements influence the secretion of saliva and the secretory and motor functions of the stomach. In man mastication raises the metabolism by nearly 50 per cent, as compared with that in an organism at rest, and influences the circulation and muscular efficiency. All these influences are produced by complex reflexes, both conditioned and unconditioned, which form the basis for the act of eating and which influence the course of the physiological functions in the organism.

An examination of the degree to which a food substance (usually the kernel of a nut) is ground up after a certain number of masticatory movements is used in the study of mastication. The strength of the masticatory muscles is measured by special dynamometers (gnathodynamometers).

Deglutition. The act of deglutition implies the sum total of motor reactions by which the food is moved from the oral cavity through the oesophagus to the stomach. The movement of the bolus through the upper part of the oesophagus is actually felt by the eater. When the bolus enters the lower third of the oesophagus its movement is no longer felt. The act of deglutition begins under the influence of the higher divisions of the central nervous system. Movements of the tongue push the bolus to the tongue's dorsum where a groove is formed (by contraction of the tongue's muscles). Then, due to the contraction, mainly, of the mylohyoid muscle, the bolus is pressed against the hard palate and passed through the anterior pillars of the fauces. The resulting stimulation of the receptor apparatus of the soft palate causes a reflex contraction of a number of muscles, in particular, the muscles elevating the soft palate. Owing to this the oral cavity is separated from the larynx. With the elevation of the soft palate by the contraction of the *genio-hyoidei* and *tensoris veli palatini* muscles the nasopharyngeal cavity (*cavum pharyngo-nasale*), where the choanae and the openings of the Eustachian tubes are located, is sealed off. In pushing the bolus the tongue presses against the epiglottis, closing the entrance to the air passages: at the same time the hyoid bone and the larynx are elevated by the contractions of the *palatini, stylo-hyoidei* and *digastrici hyoidei* muscles. All these movements tightly close the entrance to the larynx and the return of the bolus into the oral cavity is now obstructed by the elevated root of the tongue and the pillars of the fauces pressed against it. The bolus, now in the pharyngeal cavity, can enter only the opening of the oesophagus, dilated and pushed up to the pharyngeal cavity by contractions of the *palatini* and *pterygoidei* muscles (Fig. 102, left).

After the bolus enters the oesophagus the oral and pharyngeal cavities assume their initial configuration (Fig. 102, right).

The whole process of sealing off the air passages and of the bolus' gliding through the pharynx into the oesophagus past the closed larynx is very rapid. Approximately 0.3 to 0.5 seconds after the beginning of deglutition (considering this moment to be the contraction of the mylohyoid muscle, which presses the tongue with the bolus on it against the hard palate) the food is in the oesophagus and the air passages open again. But in the beginning of each act of deglutition the air passages must be closed, hence, for a fraction of a second neither inspiration nor expiration are possible.

The oesophagus is a tube with muscular walls; in its upper part the muscles are striated, in the middle—striated and smooth, and in the lower—only smooth. When not engaged in deglutition these muscles are in a state of certain tonic contraction. It is very probable that during the first moment of deglutition this tonic contraction is inhibited and the oesophagus is, consequently, relaxed.

If the food is liquid the pressure of the back of the tongue is enough to propel it into the relaxed oesophagus and it takes 2 to 3 seconds to reach its lower end, whence it enters the stomach in a thin stream. If the swallows follow each other rapidly the oesophagus remains relaxed and the liquid flows through it under the pressure created in the pharynx and by gravity.

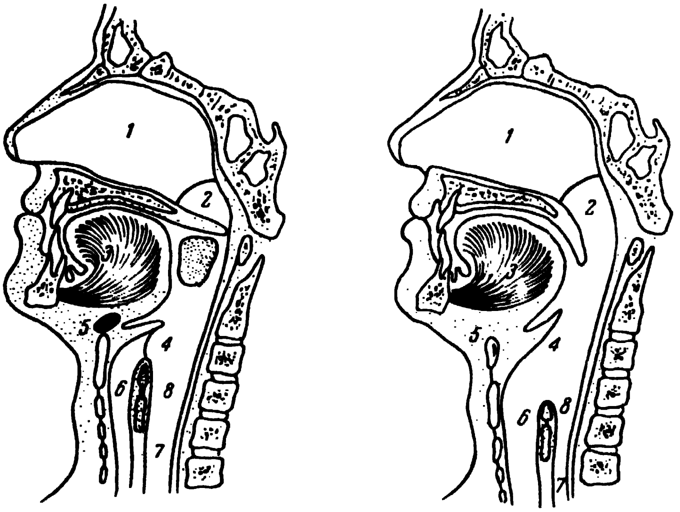

Fig. 102. Sagittal section of oral cavity and nasopharyngeal region: left—during swallowing, right—when not swallowing.

1—nasal cavity; *2*—soft palate; *3*—tongue; *4*—epiglottis; *5*—hyoid bone; *6*—thyroid cartilage; *7*—oesophagus; *8*—hypopharynx.

Left—changes in pharyngeal cavity during swallowing: bolus *(9)* is in pharynx, soft palate seals off nasopharynx; tongue and larynx are raised; entrance to latter is closed (after Arthus).

It is different if the bolus is more or less solid. In this case the passage of the food from the lower part of the pharynx into the oesophagus is aided by contractions of the middle and lower constrictors of the pharynx. The food passes down the oesophagus because of the latter's peristaltic movements which resemble the movements of a worm: the part of the oesophagus immediately above the bolus contracts, while the one immediately below relaxes and the bolus is pressed, as it were, into the part of the oesophagus which opens before it. The passage of the bolus through the oesophagus to the stomach takes 6 to 8 seconds. Deglutition ends with the relaxation of the cardiac sphincter at the entrance to the stomach.

Deglutition is a typical complex-reflex act. Both contraction and relaxation of the muscles of the upper divison of the swallowing apparatus, including the soft palate, involve the activity of the cerebral cortex. The moment the food passes the palatine arches the process becomes involuntary, i.e., independent of the cerebral cortex.

Deglutition requires that the receptors of the soft palate be stimulated. If the soft palate is smeared with novocain, deglutition becomes impossible until the anaesthesia wears off. Stimulation of the receptors of the soft palate is transmitted to the medulla oblongata, where it is transferred to the efferent neurons of the trigeminal, hypoglossal, accessory spinal and vagi nerves which innervate the mylo-hyoid muscle, the tongue and the muscles of the pharynx and larynx. The bolus, entering the oesophagus because of the contraction of these muscles, stimulates the receptors of its mucous membrane, which, reflexly again, causes the muscles of the oesophagus innervated by fibres of the vagi and sympathetic nerves to contract. Stimulation of the receptors of the muscles contracting in the upper part of the oesophagus causes a reflex relaxation of the part immediately below.

In the act of deglutition we, thus, have a series of cycles, each of which is made up of a series of processes; the consummation of each cycle leads to the stimulation of the receptors, which reflexly stimulate the following phase of the process (chain reflex).

The complicated coordinated activity of the oesophageal muscles, as well as of the other muscles taking part in the act of deglutition, is based on the complex relations in the different divisions of the central nervous system involving the structures from the medulla oblongata to the cerebral cortex. The last neuron, which sends efferent fibres to the muscles of deglutition, lies in the medulla oblongata. Its destruction makes deglutition impossible; it is, therefore, believed that the centre of deglutition is in the medulla oblongata.

During deglutition the respiratory centre is inhibited (the urge for inspiration is suppressed) and the heart rate somewhat increases. Contraction of the oesophageal and pharyngeal muscles also stimulates contraction of the muscles of the stomach by means of interoceptors.

CHAPTER 26

DIGESTION IN THE STOMACH

From the oesophagus the food enters the stomach, where it is retained for a long time and is subjected to mechanical action and the action of gastric juice.

The human stomach can hold several kg. of food and water.

The mucous membrane of the stomach is abundantly lined with small cells whose microscopic excretory openings can be seen throughout the mucosa from the entrance (cardia) to the pyloric part of the stomach. The numerous (about 14,000,000) glandules are distributed in the mucosa unevenly and their structure is not everywhere the same. In the region of the lesser curvature, on the bottom and in the body of the stomach these glandules are made up of three types of cells: the *chief*, which form the main mass of the gland's parenchyma, the *accessory*, which resemble mucous cells in structure, and the *parietal*, scattered along the gland tubule. The parietal cells are surrounded by a network of capillaries, which also penetrate to the chief cells. The glands in the region of the pylorus have no parietal cells. It is considered quite probable that some enzymes are produced only by the chief cells, while hydrochloric acid is produced only by the parietal cells. The work of Y. Lazovsky indicates, however, that these types of cells are closely related, since in the embryo the chief cells develop from the accessory and may, under certain conditions, acquire their initial properties in the adult, then secreting mucus rather than the serous substance.

The powerful musculature of the stomach is not equally developed in all of its parts. For example, a circular muscular layer is strongly pronounced in its pyloric part.

Methods Used in Studying Gastric Secretion

It was impossible to obtain natural gastric juice in large amounts until Pavlov and Shumova-Simanovskaya added an oesophagotomy to the gastric fistula in 1889.

In this operation the oesophagus is cut in the cervical part and its severed ends are grafted to the corners of the skin wound. When such a dog eats, all the food with the secreted saliva drops out of the end of the oesophagus, which is brought to the exterior of the neck, and does not get into the stomach (experiment of "sham feeding") (Fig. 104). Sham feeding causes an enormous amount of pure gastric juice, unmixed with either food or saliva, to be excreted through the gastric fistula.*

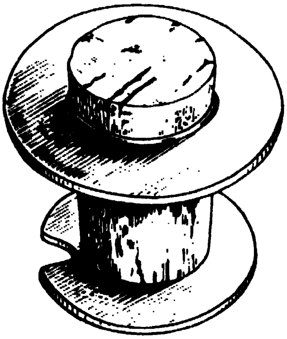

Fig. 103. Gastric fistula tube.

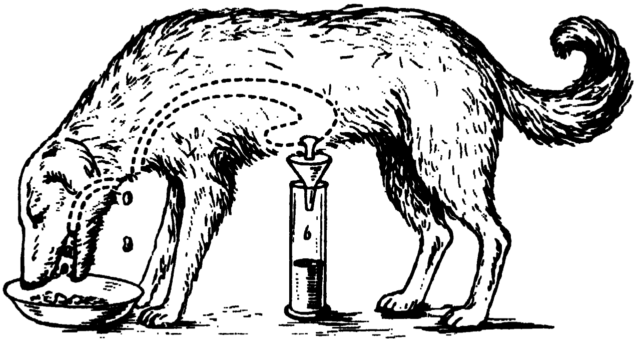

Fig. 104. Sham feeding of oesophagotomized dog with gastric fistula.

The method proposed by Pavlov enabled the investigators to secure unlimited amounts of gastric juice, but did not make it possible to study the secretion of gastric juice under normal conditions when the food consumed had been in the stomach for a long time.

To study the secretion of gastric juice Heidenhain proposed in 1878 a method consisting in the formation of a "gastric pouch" made of a strip of tissue cut out of the wall of the stomach (Fig. 105, left). The stomach was then sutured and gastric digestion could be carried on normally. By this method the food consumed did not get into the isolated pouch, and the juice, secreted to the exterior through an opening made in the skin, was free of admixtures. Heidenhain's method had a very essential drawback. however, because when the strip of tissue necessary for the formation of the pouch was shaped the nerve conductors were severed and the pouch was denervated.

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* A "factory" of gastric juice was organized at the Institute of Experimental Medicine (Leningrad) on Pavlov's initiative. The "factory" is still running with oesophagotomized dogs sham-fed daily. The pieces of meat swallowed by the dogs drop out and are swallowed by the animals again, thus making it possible to conduct sham feeding for more than an hour with a small amount of meat. The method enables the students to collect close to a litre of pure juice from each animal, which after additional purification is very successfully used in the clinic in disorders of gastric secretion. The oesophagotomized dogs live for years. They are fed by solid food put directly into the stomach through the fistula; liquid is poured through the lower opening of the oesophagus.

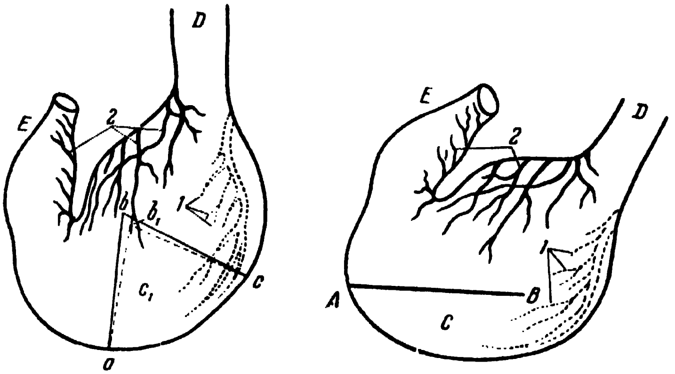

Fig. 105. Incisions for forming isolated stomachs: right - after I. Pavlov, left—after R. Heidenhain.

D - oesophagus; *E* - pyloric antrum; *1* and *2* - anterior and posterior vagal gastric plexes respectively; *C* and C_1 - strips of gastric wall out of which pouch is made; *AB* - section, according to Pavlov, retaining nerve fibres running to strip *C* (shown by dotted lines); abb_1c—section, according to Heidenhain, cutting nerve fibres running to strip C_1.

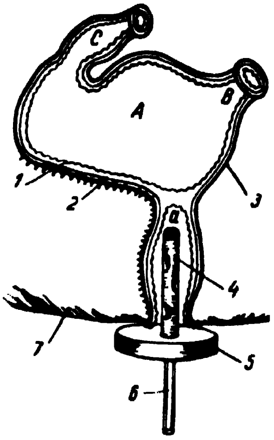

Fig. 106. Isolated pouch (after I. Pavlov).

1 - mucosa; *2* - muscular layer; *3* - serous layer; *4* - rubber tube on cork *(5)* with glass tube *(6)* for juice to run out of the cavity of the pouch *(a)*; *7* - skin of abdominal wall. Between cavities of pouch *(a)* and stomach *(A)* there is a double layer of mucosa which completely separates them; the vagal fibres are not cut; suture is seen on muscular and serous layers on left side of stomach and pouch; *B* - cardia; *C* - pylorus.

This drawback in Heidenhain's operation was eliminated by Pavlov, who proposed in 1894 an entirely new method of cutting out a gastric pouch in which the innervation remained intact. Pavlov made an incision for shaping the strip of tissue parallel to the course of the nerve fibres (Fig. 105, right). Between the strip of tissue formed by this cut and the rest of the stomach there remained a bridge of a serous muscular layer with branches of the vagus and vessels running to the pouch. The pouch was separated from the stomach only by the mucous membrane (Fig. 106).

After the operated animal recovered it was possible to observe the secretion of pure gastric juice from the pouch which retained its usual innervation. The function of the stomach is not affected to any appreciable extent since the surface of the mucous membrane of the pouch does not ordinarily exceed one-tenth to one-fifteenth of the total mucous membrane of the stomach. Numerous tests have shown that the pouch retaining the innervation and nourishment through the nerves and vessels, which run to it in the submucous membrane, exactly reflects the work of the stomach.

The pouch was shaped from the large curvature of the stomach, as well as from its pyloric part. A pouch from a strip of tissue of the lesser curvature and another pouch from a strip of tissue of the greater curvature were formed in the same dog recently after Pavlov's method in the laboratory headed by Bykov. On animals operated in this manner it is possible to observe the secretion of the glands located in different regions of the mucosa and to study the interrelation of the secretory activity of the different parts of the stomach.

Pavlov's operation of the pouch is a masterpiece of surgical art connected with physiological experiments. This method of studying the secretion of the gastric glands is still the most perfect in our country and in all the laboratories of the world.

To secure gastric juice and study the process of secretion a rubber tube is inserted through the oesophagus (swallowed). The stomach content is pumped through the tube either once after the test meal (for example, Boas-Ewald's breakfast—50 gr. of dry bread in a glass of tea without sugar) or repeatedly for 2 to 3 hours after placing some stimulant (broth, vegetable juice, a weak alcohol solution, or a 5 per cent solution of caffeine) into the stomach through a tube.

Pure human gastric juice without admixtures can be secured by mechanical stimulation of the stomach wall. A double tube is inserted into the stomach for this purpose (Fig. 107). The external tube is topped by a spherical rubber balloon, which mechanically stimulates the stomach by inflation; the secreted pure gastric juice is pumped out through the inner tube. This method, developed in Bykov's laboratory, makes it possible to secure obout 100 to 300 ml. and even 1,000 ml. of pure juice in 2 hours and to watch the entire process of its secretion. The perfection of this method has, of late, enabled investigators to determine the secretory and motor functions of the human stomach, which is of great importance in diagnosing the disorders of the digestive organs (Kurtsin).

Composition of Gastric Juice

Pure gastric juice of man and animals (dog, cat) is a colourless, transparent liquid of an acid reaction (pH = 0.8 to 1.0) due to the *hydrochloric* acid it contains (0.2 to 0.5 per cent). It has a low specific gravity (1.0083 to 1.0086 in man). Gastric juice contains a small amount of mucus, which varies with the stimulus causing its secretion.

Of inorganic constituents gastric juice contains, primarily, potassium chloride and sodium chloride; it also contains ammonium chloride and a small amount of phosphates, sulphates, Mg and Ca. Traces of thiocyanic compounds are found in the human gastric juice.

The organic constituents of gastric juice are, primarily, protein compounds and small amounts of lactic acid, glucose, creatine, phosphoric and adenosine phosphoric acid, urea and uric acid. These compounds are products formed during the normal secretion of gastric juice (Vasyutochkin) rather than products of fermentation.

The protein part of the organic substances in the gastric juice is composed mainly of enzymes, the most important of which is *pepsin*, which converts the proteins into albumoses and peptones. The chief cells of the gastric mucosa produce pepsin in an inactive (zymogenous) state; pepsin becomes active only in the presence of an acid. In an alkaline medium pepsin is totally inactive. The content of pepsin in gastric juice is determined by its action on proteins; the method developed by Mett in Pavlov's laboratory (Mett's tubes) is often used for this purpose.

In addition to pepsin the gastric juice in young individuals also contains rennin—*chymosin;* this enzyme curdles milk in acid, neutral and alkaline media. Pavlov ascertained that in the gastric juice of an adult organism it was not chymosin but pepsin that curdled the milk.

The third enzyme in the gastric juice is *lipase*. Under the action of lipase the neutral fats are split up into fatty acids and glycerol. Lipolytic action in the stomach of adults is weak, while in sucklings this process is of great importance. Lipolytic enzymes brought from the intestines may act in the contents of the stomach.

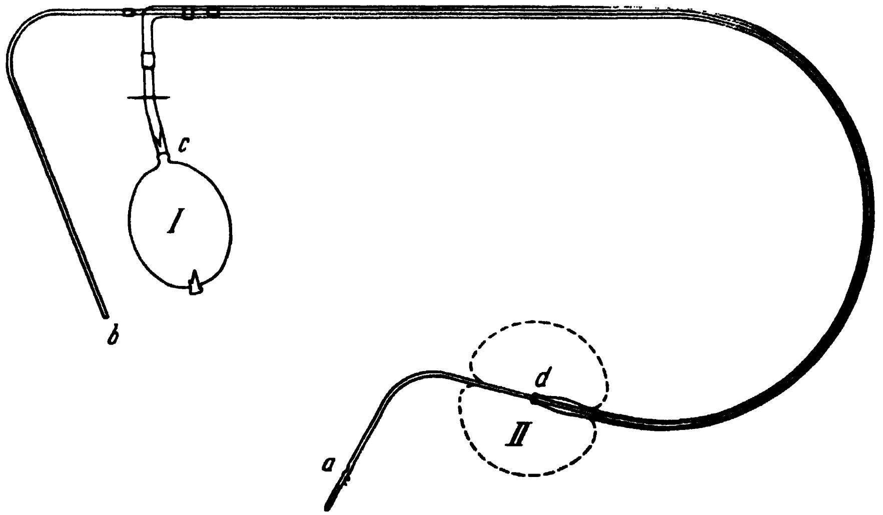

Fig. 107. Double stomach tube for collecting gastric juice secreted in response to mechanical stimulation of stomach.

Inner tube *ab* serves to collect secreted gastric juice (through opening *b*). Through outer tube *cd* air pumped by syringe (I) enters and inflates balloon (II) inserted in stomach (after I. Kurtsin).

Owing to an abundance of hydrochloric acid gastric juice has bactericidal properties.

The hydrochloric acid of the gastric juice is secreted by the cells of the mucous membrane of the stomach in a rather constant concentration. though the juice, which flows to the exterior, differs in its hydrochloric acid content. This, as the experiments in Pavlov's laboratory have shown, depends on the different rates of secretion. When secreted slowly, the gastric juice is in large measure neutralized by alkaline mucus, which is secreted by the accessory cells in the mucous membrane of the stomach; in rapid secretion it is hardly neutralized at all. It is not improbable that the HCl content is also regulated in the very course of the secretory process in the various glandular cells.

The mucous membrane of the lesser curvature produces a juice which has a stronger converting effect on proteins than that secreted by the cells of the greater curvature.

The pyloric juice, which has an alkaline reaction (pH = 7.8 to 8.4) and an inactive pepsin (at the above pH) digests proteins only if a 0.2 to 0.5 per cent solution of hydrochloric or some other acid is added. The digestive power of this juice is low, and the little clots of mucus in it contain more enzymes than the liquid part of the juice.

Gastric juice digests various tissues including the *excised* wall of the stomach. It is not yet clear why the wall of the stomach is not digested by the gastric juice it secretes. There are several views in reference to this: some believe the mucus, lining the stomach wall, to be a protective coating; according to others the blood circulating through the glands, being of an alkaline reaction, prevents the action of pepsin; still others think there is an enzyme—antipepsin—in the walls of the stomach, which paralyzes the action of pepsin. It is also possible that normally the gastric juice does not act on the mucous membrane because in the lipoids of the cell membrane hydrochloric acid, which activates pepsin, is in a weakly dissociated state and becomes strongly dissociated only in a water solution.

The question why the stomach wall is not digested by the gastric juice is very essential, because its solution would help in the study of ulcers, which arise when the normal activity of the glandular apparatus in some portion of the stomach (most frequently in the lesser curvature) is impaired. The glands work under the influence of nerve stimuli, which originate in both the lower and higher divisions of the central nervous system as a reaction to the stimulation of the receptors located in the organs of the digestive tract (interoceptors) and of the innumerable exteroceptors (eye, ear, nose, skin, etc.). An impairment of this complex regulating apparatus of the stomach, mainly of its most excitable portion—the central nervous system—leads to disorders of the secretory process. Thus most of the pathological processes in the activity of the secretory and motor apparatus of the stomach arise. Derangements in the work of the glands are attended by disorders of the supply of the glands with nutritive materials owing to changes in the blood and lymphatic vessels.

Secretion of Gastric Juice

Pavlov ascertained that the glands of the stomach did not work incessantly, but only under the influence of special stimuli. Some investigators found juice also in an empty stomach under laboratory conditions and in the clinic without the use of any stimuli, but a thorough check-up on these observations led to the conviction that the so-called "spontaneous secretion" was caused either by the action of stimuli in some way connected with eating, or by a secretion connected with a stimulation of the mechanoreceptors of the stomach, or, finally, by a secretion resulting from products formed in various pathological changes in the organism, for example, an abscess, osteomyelitis and other diseases (investigations of I. Razenkov's laboratory).

The reaction of the stomach content in the absence of a stimulus, which causes secretion, is usually alkaline due to the mucus constantly secreted by the accessory cells of the gastric glands. Intestinal juices and content, regurgitated here from the duodenum, are nearly always found in the stomach contents secured through a tube.

The agent, which causes secretion of gastric juice, is, primarily, a complex of stimuli, connected with the act of eating, i.e., stimulation of the receptors in the oral cavity and the receptors stimulated by the natural conditioned stimuli (sight and smell of food, etc.). It is very easy to ascertain that the act of eating causes secretion of the gastric glands independently of the food getting into the stomach by registering the gastric juice secretion in "sham feeding" of an oesophagotomized dog whose food does not get into the stomach. In sham feeding, as well as in ordinary eating, secretion of gastric juice begins 5 to 6 minutes after the animal is fed or is teased by the sight or smell of the food. This period between the action of the food stimulus and the beginning of secretion is usually called the *latent period* of gastric secretion.

Once begun, juice secretion rapidly increases and reaches its maximum within the first or second quarter of an hour after eating. The course of juice secretion corresponds to the kind of food consumed. If the animal is given 200 gr. of raw meat, or 200 gr. of white bread, or 600 ml. of milk, it is easy to see that each kind of food has its corresponding latent period, that the course of secretion differs in all three cases and that a different amount of juice is secreted during the entire secretory period in each case. The secretion, which starts within 5 to 9 minutes after the beginning of meat and bread eating, reaches its greatest value during the first hour, i.e., rapidly (especially when meat is eaten); in the third hour after meat eating and in the second hour after bread eating the secretion considerably decreases, in the latter case remaining on a low level for a long time. When the animal is fed milk, the secretion increases gradually, reaches the highest level only in the second or third hour and then gradually drops to zero. The duration of the secretory period after taking the above-mentioned foods also differs: an average of 6 to 7 hours after eating meat, 8 to 10 hours after bread, and 6 hours after milk (Fig. 108). The greatest amount of juice is secreted after ingestion of meat, and much less after bread and milk. The acidity of the juice varies with its amount.

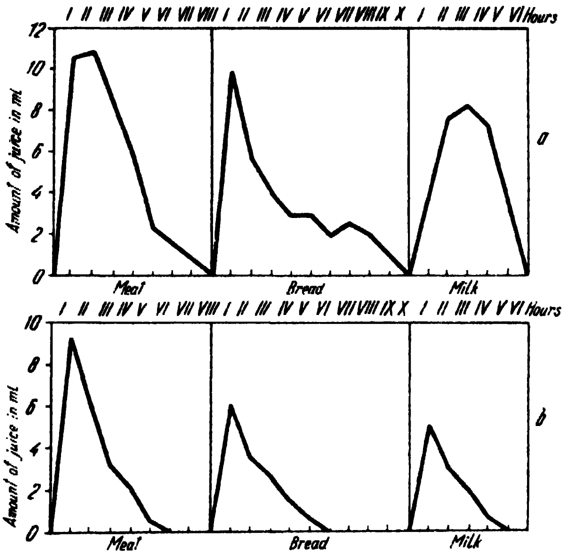

Fig. 108. Secretion of gastric juice in the dog after various foods: top—from pouch of greater curvature (after I. Pavlov); below—from pouch of lesser curvature (after K. Bykov).

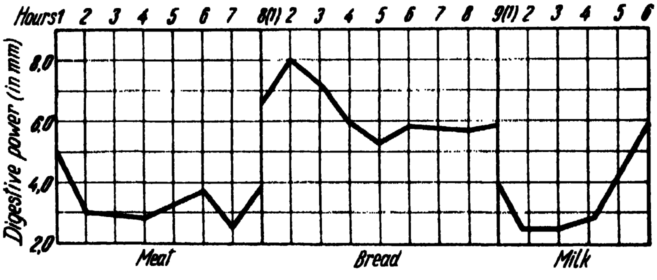

Fig. 109. Fluctuations in digestive power of gastric juice by the hour.

According to Mett's method the digestive power of the juice is expressed in millimetres of digested protein inserted in Mett's tubes (after I. Pavlov).

Each type of food stimulates secretion of a corresponding juice with a definite digestive power (Fig. 109).

The curve of juice secretion from a Pavlov pouch in the lesser curvature runs a peculiar course (Fig. 108 *b*).

The dependence of the secretion of gastric juice on the type of stimulus may be expressed in a table showing the influence of various foods on the different aspects of gastric secretion (Table 10).

The amount of juice secreted during the entire secretory period, *when the same kind of food is eaten*, is directly proportional to the amount of food consumed; if the amount of food be doubled the amount of juice secreted also doubles. The time the food stays in the stomach is approximately proportional to the square root of the amount of food.

Table 10

Amount of juice	Acidity of juice	Digestive power of juice	Duration of juice secretion
After meat more than after bread	After meat higher than after milk	After bread greater than after meat	After bread longer than after meat
After bread more than after milk	After milk higher than after bread	After meat greater than after milk	After meat longer than after milk
After milk less than after meat or bread	After bread lower than after meat or milk	After milk lesser than after bread or meat	After milk shorter than after bread or meat

Mechanism of Gastric Juice Secretion

Complex-Reflex Phase of Gastric Secretion

The foregoing figures and curves showing the course of the secretion of gastric glands when different foods are ingested require an analysis of the mechanism which conditions gastric secretion. The point of departure for the understanding of this mechanism should be the abundant secretion of gastric juice in *sham* feeding, i.e., during the stimulation of the receptors in the oral cavity and the pharynx by foods (the food does not reach the stomach, because its pieces drop out through the cut in the oesophagus). In addition to the receptors in the oral cavity and the pharynx the olfactory and visual receptors are also stimulated during eating. Abundant secretion of gastric juice by stimulation of the oral cavity with food during its mastication and deglutition has also been demonstrated in people in whom gastric fistulas were made to ensure feeding because of oesophageal stricture. If such people masticate and swallow food, which is ejected before reaching the stomach, a considerable amount of pure gastric juice is secreted (up to 100 ml. per hour).

The secretion of gastric juice as a result of the stimulation of the receptors in the oral cavity in the act of eating is an unconditioned reflex, but conditioned reflexes, connected with the action of food on the taste, olfactory, visual and other receptors, also manifest themselves at the same time. This shows that the secretion of gastric juice (like all the usual reflex phenomena) is a complex-reflex act, i.e., a combination of conditioned and unconditioned reflexes. This phase of gastric juice secretion is, therefore, designated as the complex-reflex phase.

The *efferent* fibres, which innervate the gastric glands, run in the trunk of the *vagus*. After both vagi in the neck are cut juice secretion in the stomach during sham feeding ceases. But the stimulation of the vagus in an acute experiment causes, as Pavlov ascertained, abundant secretion of the gastric glands. It follows that secretion of gastric juice as a result of the stimulation of the receptors in the oral cavity with food is an unconditioned reflex, whose reflex arc is composed of: a) receptors in the oral cavity and other receptors, b) afferent fibres running from these receptors as part of lingual, glossopharingeal, superior laryngeal nerves and other afferent conductors, c) reflex centre in the region of the medulla oblongata and centres located higher, including the cerebral cortex, and d) efferent parasympathetic fibres running in the trunk of the vagi and stopping at the ganglionic cells located in the wall of the stomach (Auerbach's plexus).

Secretory fibres to the gastric glands also run as part of the splanchnic nerve; they are sympathetic fibres. Their stimulation in an acute experiment causes little secretion of the gastric glands (Y. Volborth). Cutting the sympathetic fibres, however, does not appreciably affect gastric secretion, but, if the vagi are cut, these fibres are not enough to ensure normal secretion of the gastric glands in the act of eating. Cutting the splanchnic nerves sharply affects the production of mucus in the stomach, which is increased not only in the accessory cells, but also in the chief cells (I. Razenkov's laboratory).

Gastric secretion at the sight and smell of food is a result of a natural conditioned reflex. which arises in the distal receptors and is developed on the basis of the unconditioned reflex, caused by the stimulation of the oral cavity, involving the cerebral cortex. Gastric juice secreted at the sight and smell of food, under the action of food signals in general, is often termed "trigger juice" because it can be secreted even before food is taken. Its amount and acidity are somewhat lower than in the secretion caused by food.

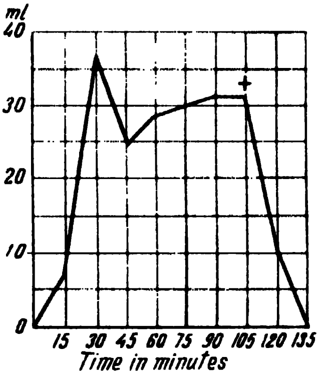

Fig. 110. Curve of secretion of pure gastric juice in response to mechanical stimulation of th [illegible] ach in man with gas-[illegible]oesophagostomy.

[illegible] sign stimulation consisting [illegible] flation of a balloon, inserted i[illegible] stomach, was discontinued (after I. Kurtsin).

Juice secretion in the stomach during the complex-retlex phase can be easily inhibited, for example, by pain stimuli.

Second phase of gastric juice secretion (influence of mechanical stimulation on gastric secretion). The question whether the mechanical factor was a stimulus of the gastric glands was debated for a long time. By pumping juice from an empty stomach through a tube some physiologists and many clinicists pointed out the importance of mechanical stimulation in exciting the glands of the stomach. Pavlov disputed this fact at first, but S. Chechulin showed on dogs and later Kurtsin and Slupsky demonstrated by observation of people that the mechanical stimulation of the mucous membrane of the stomach caused the gastric glands to act. Inflation of a small balloon (of thin rubber), inserted into the human stomach, produces abundant secretion of gastric juice approximately 5 minutes after the mechanical stimulation is started (see Fig. 110). The secretion of juice begins immediately with a sharp rise of the curve and remains on a high level as long as the balloon is inflated. As soon as the balloon is deflated secretion of the juice rapidly decreases. If a person is shown palatable food and at the same time the balloon, inserted into his stomach beforehand, is inflated, the amount of gastric juice secreted will be much greater than that secreted when only the food is shown. Apparently, when the food is shown and the balloon is inserted a complex of stimuli comes into play from the receptors of sight and smell and the receptors in the wall of the stomach.

Chechulin has shown that the secretion of gastric glands in response to mechanical stimulation of the mucous membrane is caused reflexly owing to the excitation of the receptor apparatus located deep in the wall of the stomach. The efferent fibres starting the secretion in response to the stimulation of these receptors run in the trunk of the vagi.

During sleep and under anaesthesia mechanical stimulation of the stomach causes much lesser secretion of the gastric glands than in the waking state. It may be assumed that stimulation of the interoceptors of the stomach not only provokes the unconditioned reflex, because the excitation of the afferent paths is transmitted to the cell bodies of the efferent neurons of the vagi in the medulla oblongata, but also acts as a signal of the unconditioned reflex which is always caused by the act of eating. Hence, in mechanical stimulation the excitation of the glands may also be considered a complex-reflex act, which includes both the unconditioned and conditioned reflexes.

It follows that another powerful stimulus of a reflex nature is added to the stimuli in the act of eating—the mechanical stimulation resulting from filling the stomach with food of different consistency and volume.

Properties of the glands of the lesser curvature of the stomach. Secretion in the Pavlov pouch formed from a strip of tissue of the lesser curvature and retaining the innervation begins and ends quicker than the secretion of the cells of the greater curvature (Bykov's laboratory). The juice of the lesser curvature contains more enzymes. Apparently, the secretory process in the stomach always begins in the glands of the lesser curvature and then spreads to the other portions of the mucous membrane. The lesser curvature may, in this respect, be considered the leading part in the secretory apparatus of the stomach. This also corresponds to the data of a morphological investigation (laboratory headed by Razenkov), which show maximal changes in the structure of the glandular cells after sustained secretion (in sham feeding) precisely in the glands of the lesser curvature. These changes are expressed mainly in loss of the granules by the cells.

Chemical Stimuli of Gastric Secretion

In addition to mechanical stimulation the glands of the stomach are also stimulated by *chemical agents* contained in the foods or produced by them during digestion and their subsequent entrance into the blood.

The existence of chemical agents, which stimulate secretion in the stomach, is proved by the fact that insertion of meat and other substances directly into the stomach causes juice to be secreted, though this occurs much later (30 to 60 minutes later). Since stimulation of the receptors in the oral cavity and the action of conditioned food stimuli are absolutely excluded and since this secretion is observed also in a denervated stomach, it must be assumed that secretion of the juice is caused here by some *chemical agents*, apparently, acting through the blood, primarily, on the nervous apparatus of the secretory cells themselves.

Secretion of gastric juice under the action of chemical stimuli results when a number of food substances enter the stomach, namely: 1) products of the digestion of proteins (peptones), 2) extractive (i.e., water soluble) substances contained in meat and vegetables, and 3) weak alcoholic solution. A small amount of gastric juice is secreted when water, saliva, bile and weak solutions of acids enter the stomach. Strong meat, fish and vegetable broths produce the strongest juice-secreting action of all the food substances which contain chemical stimuli.

The chemical stimuli act as follows: when the above-mentioned substances enter the stomach some compounds enter the blood and, brought with it to the neuroglandular apparatus of the stomach, stimulate the latter. The nature of these substances, which act in a humoral way, is not quite clear. Razenkov has shown that it is enough to inject the blood of a fed dog into the blood of a hungry dog to cause gastric secretion in the latter. Razenkov, therefore, believes that the products of digestion of the food substances, which entered the blood, are capable of stimulating the gastric glands. It is quite probable that histamine plays a big part. This assumption is based on the fact that injection of histamine into the blood causes very strong gastric secretion (1 to 1.5 mg. of histamine is sufficient for man). It is possible that histamine is formed in the stomach at the endings of the vagus. It should be noted that the stomach is the only organ where there is no histaminase, the enzyme which splits up histamine.

There are also indications that the wall of the pyloric antrum produces *gastrin*, a special compound of a polypeptide nature, when acted upon by substances which are chemical stimuli of gastric secretion; this compound, brought to the gastric glands with the blood, stimulates them. It is important to note in connection with this that, according to the data of Pavlov's laboratory, the chemical stimuli of gastric secretion cause the secretion *only* when they act on the mucous membrane of the *pyloric antrum*. However, this problem is not clear yet, because Razenkov found no essential changes in gastric secretion after a surgical removal of the pylorus, whereas other investigators (V. Savich and Y. Volborth) did find them. A. Solovyov has recently obtained facts which show that the chemical stimuli act through the nervous apparatus of the stomach. In its turn the local intramural nervous system of the stomach and the intestines is connected with the central nervous system through the vagus and the sympathetic nerves.

Secretion of gastric juice under the action of chemical agents has long since been designated by Pavlov as the neurochemical phase of secretion. Since the chemical substances develop their juice-producing action first in the pyloric antrum and then in the intestines, Pavlov divided the neurochemical phase into two phases: the pyloric and the intestinal. The juice secreted during the neurochemical phase of gastric secretion has a lesser digestive power and a lower acidity than the juice secreted during the complex-reflex phase.

Synthesis of the Juice-Secretion Curve

Juice secretion in the normal process of digestion is the sum total of the influences of various stimuli acting on numerous receptors in which conditioned and unconditioned reflexes arise.

To prove this thesis we may draw the curve of juice secretion from the Pavlov pouch when 200 gr. of meat have been eaten (Fig. 111 *a*) and when both phases of the secretion are on hand. In another series of experiments it is possible separately (Fig. 111 *b*) to draw a curve of juice secretion after placing unnoticeably for the dog 200 gr. of meat into its stomach; then we have only the action of the mechanical stimulation of the stomach and the second phase of secretion on hand, since the stimulation of the exteroceptors, which are excited in the act of eating, is in this case excluded.

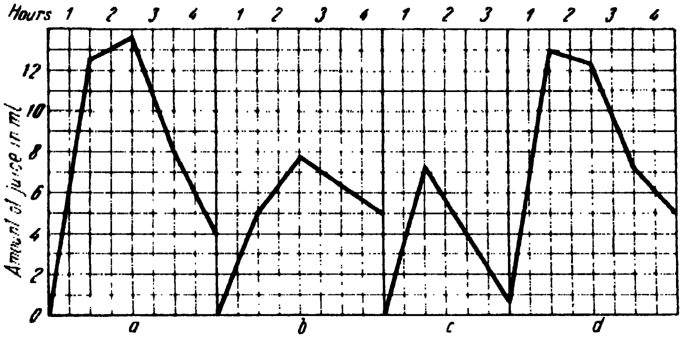

Fig. 111. Curves of gastric juice secretion in the dog.

a — after consuming 200 gr. of meat; *b* — after insertion of 200 gr. of meat into stomach; *c* — in sham feeding; *d* — synthetic curve obtained by adding *b* and *c* (after I. Pavlov).

Finally, we can draw a curve of juice secretion by a third series of experiments in sham feeding, when only the first phase is on hand (Fig. 111 *c*). The synthetic curve of juice secretion (Fig. 111 *d*), obtained by adding the two last curves together, practically coincides with the curve of secretion in meat eating.

Effect of Fats and Salts on the Activity of the Gastric Glands

When neutral fat enters the stomach it *inhibits* the work of the gastric glands during the first 2 to 3 hours and causes secretion of a weak digestive juice during the subsequent hours (Fig. 112). The inhibiting influence of neutral fat on the gastric glands is at times so strong that the fat used together with other stimuli almost completely inhibits the secretion for some time after the intake of mixed food. However, strong stimuli of gastric secretion, such as broth or vegetable juices, can disinhibit the depressing effect of the fat (Leporsky, Bykov).

The depressing effect of the fat cannot be explained by local causes because inhibition of gastric secretion develops only after the fat enters the duodenum from the stomach. The inhibiting action of the fat does not develop after the vagi are cut (Orbeli and Tonkikh). It follows that inhibition of gastric secretion after an intake of fats is conditioned by a reflex from the receptors in the duodenum stimulated by the action of the fat. Some authors ascribe the inhibiting effect of fat to a special hormone. If such a hormone does exist it, probably, acts through the nervous apparatus of the glands.

The stimulating effect of fat during the second phase of its action must be attributed to the products of fat conversion and transformation; in this respect glycerol has proved inactive, whereas the fatty acids and the soaps stimulate the gastric glands.

Solutions of soda, oleic acid, hydrochloric acid in a sufficiently strong concentration (more than 0.5 per cent) and strong solutions of salts must also be considered as agents inhibiting gastric secretion. All these substances (except HCl) depress gastric secretion only when they enter the duodenum; the receptor surface here is the mucosa of the intestine from which, in these cases, inhibition of gastric secretion is caused, whereas hydrochloric acid acts from the region of the pyloric antrum.

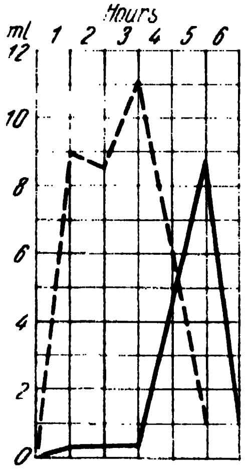

Fig. 112. Secretion of juice from isolated gastric pouch, when 10 ml. of olive oil is intro duced into large stom ach, and variation in amount of liqui contained in it. Contin uous line shows secre tion of gastric juice dotted line show changes in amount o the gastric content (th latter is shown on scale 1/100 of that the curve of juice

Mechanism of Gastric Secretion with Different Kinds of Food

By evaluating the significance of the complex-reflex phase, which takes place when various extero- and interoceptors are stimulated, it is possible to explain the peculiarities of gastric juice secretion after eating different kinds of food. The sharp rise of the curves of juice secretion during the first hour after eating different kinds of food is conditioned in all cases by the action of the stimuli on the receptors in the oral cavity and on the receptors in the wall of the stomach. It is probable that when meat is eaten this stimulation is stronger, since the latent period in this case is somewhat shorter and the rise of the curve of juice secretion is the steepest. The curve of juice secretion after milk is consumed rises slower than when meat or bread are eaten because the fat contained in the milk quickly inhibits the secretion.

The subsequent course of juice secretion after the consumption of different kinds of food is explained as follows. When meat is consumed the appearance in the stomach of extractive substances of meat, as well as peptones, which were produced by the action of pepsin on the proteins, serves as an impetus for the second phase, which is strongly pronounced during the second and third hours after meat or generally protein food is eaten and which gradually fades as the amount of chemical stimuli decreases. When carbohydrate food (bread and other substances) is eaten the work of the glands, which vigorously develops under the influence of the act of eating, sharply decreases beginning with the second hour after eating and remains on a low level for a long time (8 to 9 hours). This is explained by the fact that there are very few chemical stimuli in bread (these are only the products of digestion of a small amount of proteins contained in bread). It is very probable that the low secretion for a long period after bread is eaten (as well as potatoes and other substances) must be ascribed to the mechanical stimulation of the receptors of the stomach, the more so since many experiments have ascertained the dependence of the nature of the secretion on the physical structure of the food substance. Black bread (and large pieces of any food) causes more vigorous secretion of gastric juice than finer sorts of bread or better ground food.

The peculiarities of the secretion curve when milk is consumed are explained, as has already been said, by the inhibiting action of the fat contained in the milk. The juice-producing action of the fatty acids, formed from the fat, as well as the action of the products of digestion of the milk proteins begins, however, during the second or third hour after the consumption of milk. The inhibiting action of the fats ceases by this time and the maximum of secretion is, therefore, observed 3 to 4 hours after the consumption of milk.

Secretion in the Pyloric Region and of Brunner's Glands in the Duodenum

Glands in the pyloric region. These glands secrete juice of a mildly alkaline reaction (about 0.05 per cent $NaHCO_3$) containing pepsin and (according to I. Razenkov) a special glycolytic enzyme which converts glycogen into lactic acid. The pyloric glands secrete juice incessantly. The mechanical stimulation of the pyloric mucosa increases the activity of its glands. The act of eating does not increase the secretion of the pyloric glands; on the contrary, in the beginning of the animal's feeding it can be observed that the secretion in the pylorus decreases. Secretion of the pyloric glands increases when fats act locally on the pyloric wall and is inhibited when fats. HCl and fatty acids enter the duodenum. Since HCl reflexly shuts off the pylorus when it enters the duodenum, it may be said that the secretion of the pylorus is depressed when the contraction of its sphincter separates the pylorus from the intestine. In conformity with this the substances, which do not cause the pyloric sphincter to contract, do not depress juice secretion from the pyloric glands, but even increase it. Such, for example, is the action of soda.

It is interesting that after the removal of the pyloric part of the stomach there is a reorganization in the glands on the bottom and in the body of the stomach, characterized by a transformation of the accessory cells into cells of pyloric glands and by a formation of mucus in the chief cells. On the other hand, when the bottom and the body of the stomach are removed the glands of the pyloric division grow extensively and replace, as it were, the excised chief cells of the stomach (Lozovsky). This process, apparently, corresponds to the changes observed in the pylorus of people who suffer from a chronic inflammation of the gastric glands (chronic gastritis).

Secretion of Brunner's glands. The secretion of Brunner's glands, located in the submucous layer of the upper divisions of the duodenum, resembles in its composition that of the pyloric glands.

The juice of Brunner's glands is a colourless syrupy mass of an alkaline reaction with an admixture of mucus. It contains pepsin which acts in a mildly acid medium. Brunner's juice acts on proteins, fats and starch; its digestive power is weaker than that of gastric juice. Brunner's glands secrete juice incessantly, the secretion varying with the intake of food or the introduction of certain substances.

The pyloric juice and the secretion of Brunner's glands are equally important. When rich food, which inhibits the juice secretion in the stomach, is consumed the juice of the pyloric and Brunner's glands, active in a mildly acid medium, dissolves the collagen of the connective tissue layers which contain the fat of the different foods.

Phenomena Attending the Activity of Gastric Glands

The activity of gastric glands, like that of other glands, is attended by a series of concomitant processes in the form of changes in the blood supply, appearance of electric currents in the walls of the stomach and by morphological changes. The work of the secretory cells of the glandular apparatus of the stomach is most closely connected with the general state of the body, particularly its chemistry, which depends on the nature of nutrition.

K. Koshtoyants studied the changes in the secretory work of the gastric glands in dogs with Pavlov pouches long kept on different foods. It turned out that when the animals were given food rich in carbohydrates for a long time the secretion decreased and the nature of the gastric juice secretion changed. Contrariwise, when the animal was fed protein-rich food for 40 to 60 days, the amount of juice increased during the chemical phase; the nature of the curve of juice secretion also changed. Similar observations were made on people where a dependence of the secretion on a sustained monotonous diet was also discovered. These data are important for dietetics.

Secretion diminishes to the point of complete cessation of secretory activity when the body is overheated. Gastric juice secretion diminishes during considerable muscular effort. Gastric secretion may vary with the activity of endocrine glands. It is well known that adrenalin and the hormone secreted by the posterior lobe of the hypophysis depress the work of gastric glands, whereas the hormone of the thyroid gland, on the contrary, intensifies it.

Thus, the endocrine glands, which are themselves stimulated by the nervous system, excite the neuroglandular apparatus of the stomach. The effect of adrenalin on gastric secretion is discovered, primarily, on a definite secretory field innervated chiefly by the sympathetic nervous system, i.e., the action of adrenalin is felt mainly in the larger curvature (Solovyov's experiments).

The action of hormones varies with the type of nervous system of the given animal or man. The same is true of other chemical stimuli used as medicines.

In different diseases not directly connected with the gastrointestinal tract the activity of the gastric glands may considerably vary with changes in body temperature concomitant with these diseases and with the products of altered metabolism.

It has been shown in the laboratory headed by I. Razenkov that the digestive glands, including the glands of the stomach, secrete protein substances, which after subsequent conversion are absorbed in the intestines and are used for the building of cells and tissues of vitally important organs. Participation of digestive glands in intermediate metabolism forms a new aspect in the activity of the digestive apparatus. This process is particularly manifest in prolonged starvation.

Secretion of gastric juice influences the chemistry of the body in general, since the secretion of the glands of the fundus and the lesser curvature of the stomach leads to the elimination of the acid products from the organism. The blood of the animal or man acquires vasodilating properties during digestion (I. Razenkov).

Water and the Activity of Gastric Glands

Water is a weak stimulant of the gastric glands. At the same time it must be borne in mind that the activity of the gastric glands, like that of other glands, requires that water and salts be supplied by the blood.

In the therapy of many diseases of the gastric glands, as well as in everyday life, mineral waters are used for drinking; these waters contain salts and gases in much greater amounts than ordinary drinking water. The salts and gases of the mineral waters considerably affect the secretion of the gastric glands, almost always intensifying their work if the mineral water is taken simultaneously with the meal or immediately preceding the meal, and depressing the secretion of the glands if the mineral water is taken half an hour or an hour before the meal.

Mineral water acts on gastric secretion reflexly both during the first and second phases of the secretion.

Movements of the Stomach

The walls of the stomach contain thick layers of smooth muscle fibres distributed in three directions—circular, transverse and oblique. At the pyloric end there is a powerful circular layer of muscle, which forms the locking pyloric sphincter. Where the body of the stomach merges into the pyloric part there is also a thickened layer of circular muscular fibres (the prepyloric sphincter), whose contractions separate the cavity of the fundus of the stomach from the pylorus. The Auerbach and Meissner plexes, which are connected with the nerve centres through the vagus and the sympathetic nerves, are located in the muscle layers and in the submucous layer.

We can record the movements of stomach with the aid of a thin rubber balloon filled with air or water, inserted into the stomach and connected with a recording device through a manometer (Fig. 113).

An important method used in the study of the stomach movements consists in X-ray observation of the contours of the stomach filled with a contrasting substance. The contours of the stomach are clearly seen and can be photographed (Fig. 114). Roentgenographic techniques make it possible not only to observe the movements of the stomach, but also to study the relief of the folds of the mucosa. The relief of these folds changes with the contraction of the *muscularis mucosae*.

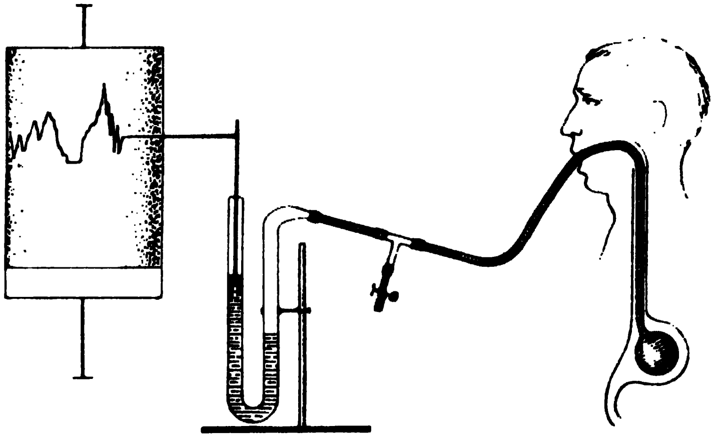

Fig. 113. Diagram of method used in recording gastric movements in man.

During contraction of the smooth muscles of the stomach a pressure develops in its cavity, reaching 140 mm. Hg in its pyloric part, where the muscles are stronger, and 40 mm. in the regions of its fundus and body.

Two types of gastric movements are distinguished: the *periodic*, conditioned by the contractions of the smooth muscles alternating with their relaxations, and *tonic*, characterized by protracted shortenings of the same muscles. In the former case the record curve of the gastric movements (Fig. 115) shows more or less large and frequent waves; in the latter case, the whole record curve is skewed upward where it remains on the same level for a long time.

The periodic (wavelike) movements of the stomach usually begin in its cardiac portion where the muscles are relatively stronger. These movements spread over the larger and lesser curvatures in the following manner: when contraction occurs at one point, the neighbouring point relaxes. Under certain conditions the contractions in the prepyloric part are so strong that the entire pyloric region, as was pointed out above, is sealed off from the rest of the stomach.

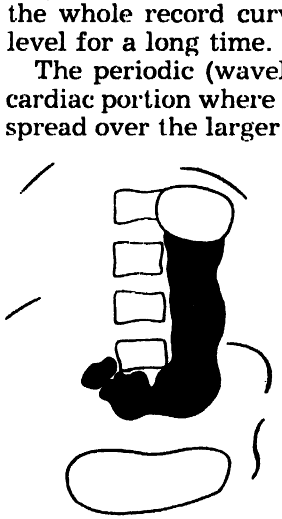

Fig. 114. Normal shape of human stomach (radiograph) (after Cannon).

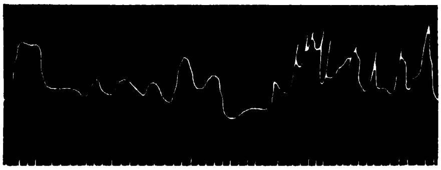

Fig. 115. Record of gastric movements in man.

Lower line marks the time (1 second).

Solid food lies for some time (2 to 3 hours) in layers piled on each other (Fig. 116). It begins to mix only after prolonged action of the gastric juice Due to the sustained tonic contraction of the stomach muscles the pressure in the fundus remains nearly constant whatever the degree of the stomach repletion. Weak, wavelike movements begin 20 to 30 minutes after the stomach is filled; the waves of contraction start in the cardiac part and at the bottom of the stomach and spread to the pylorus. These weak contractions and tonic tensions suffice to move the contents of the stomach cavity to the pylorus, especially because of the strong wavelike movements in the antrum directed towards the pylorus and repeated at definite intervals. A small fissure (*sulcus gastricus*) is formed in the lesser curvature when the muscle fibres contract at the time the food enters the stomach; at this time the pylorus comes closer to the cardia. Owing to this the swallowed liquid substances can, in a certain measure, pass through the relaxed pylorus directly into the intestine.

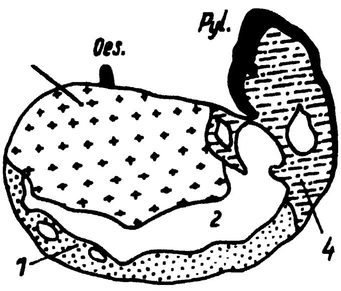

Fig. 116. Distribution of food layers in the dog's stomach 3 hours after feeding (frontal section) (after Ellenberger and Scheunert).

1—first portion of consumed food; *2*—second portion of food; *3*—third portion; *4*—food passed into pylorus.

The pyloric sphincter opens because the tonus of the pyloric muscles, which are usually in a state of constant tonic tension, relaxes. The stimuli which cause the opening and closing of the pyloric sphincter come both from the stomach and the duodenum. When the acidity of the gastric contents reaches a certain degree the sphincter opens and part of the chyme is forced into the intestine. The acid mass, getting into the intestine, mechanically distends the duodenum. The sphincter stays closed until the hydrochloric acid in the gastric contents is neutralized in the duodenum by alkaline secretions, mainly the secretion of the pancreas, and until the greater part of the mass, which entered the intestine, moves further down.

It must not be thought, however, that the sphincter opens only when the chyme in the duodenum has been fully alkalized. It is well known that the acid chyme takes long to neutralize, while the emptying of the stomach does not stop with the evacuation of only one portion of its contents; when the acid of the stomach reaches a certain stage of concentration it causes the pyloric sphincter to open reflexly. In an exactly similar manner, when the *chyme* in the duodenum reaches a *certain degree of neutralization* the sphincter opens.

In addition to acidity, the mucous membrane is also acted upon by other properties of the food: its consistency, temperature and gas content (for example, CO_2). When the food is dense and is slowly digested in the stomach it takes relatively long before the first portion enters the intestine from the stomach, following which the pylorus opens periodically and new portions of the food enter the duodenum. When the food is liquid or very thin it begins to pass into the intestine within a few minutes after its consumption. In this case the stomach empties at brief intervals and the chyme enters the intestine in spurts. Liquids may enter the intestine unchanged in the stomach; warm liquids pass quicker than cold ones. Carbohydrate food passes into the intestine the fastest; an admixture of proteins somewhat retards it. Fat food is the slowest to enter the duodenum, whereas milk and dairy food pass out of the stomach very rapidly (dairy food passes from the stomach into the intestine in large masses). The rapid movement of milk and dairy products is due to the lactose they contain, which increases the peristalsis of the intestines.

The muscles of the stomach, like those of the intestines (page 290), are capable of contracting for some time after being removed from the body, i.e., when completely severed from the nerve centres. In this case the muscles contract under the influence of the stimuli of the nervous apparatus, contained in the stomach itself.

The efferent nerves carry to the stomach impulses which stimulate and regulate its work. These impulses are conducted along fibres of the vagus and the sympathetic nerves. The fibres of the vagi carry to the muscles of the stomach mainly exciting impulses, while those of the splanchnic nerve bring chiefly inhibiting impulses. However, the effect of these impulses also depends on the state of the stomach muscles.

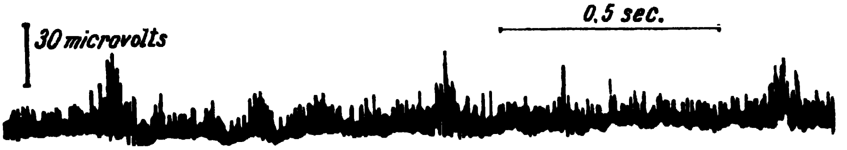

Fig. 117. Record of afferent impulses from gastric branches of the splanchnic nerve.

The afferent impulses from the receptors of the stomach and the duodenum are carried mainly in the trunk of the splanchnic (Fig. 117) and the vagus nerves (Delov). The transfer of the afferent impulses, which arise during stimulation of the gastric receptors, to the efferent impulses, that increase the contractions of the stomach, takes place on the level of the medulla oblongata and the *corpora quadrigemina*. These central apparatus are connected with the parts of the cerebrum located higher and involve the cerebral cortex.

Vigorous movements of the stomach begin at the sight or odour of food. Conditioned-reflex influences on the gastric movements may be observed when temporary bonds are formed on the basis of unconditioned reflexes in the act of mastication. Consumption of solid or liquid foods exerts different reflex influences on the motoricity of the stomach: conditioned reflexes develop, correspondingly, faster or slower.

Humoral agents also influence the gastric movements. Adrenalin, upon entering the blood, inhibits the movements of the stomach; choline and acetylcholine stimulate them.

In ruminants with their four-cavity stomachs the poorly masticated food enters, when swallowed, the paunch—the first division of the stomach—where it is moistened by its contents and from where it is thrown into the oral cavity again some time later (30 to 60 minutes). The regurgitated food is remasticated and saturated with saliva. This process takes several minutes, after which the remasticated food is swallowed again. Regurgitation and remastication are normal processes in ruminants, but in carnivores and in man regurgitation is considered a pathological phenomenon.

Vomiting

Vomiting must be considered a physiological process of a protective nature, but it may also become a pathological phenomenon.

It is an act during which the contents of the stomach and partly of the intestines are ejected through the oesophagus into the mouth and then to the exterior. This act is accompanied by a number of changes in circulation, respiration and in the muscles. Vomiting is preceded and attended by a subjective feeling of nausea. During the ejection of the gastric contents the cardia opens reflexly (Fig. 118). Pressure of the abdominal muscles and of the diaphragm ejects the gastric contents into the oesophagus, whence the contractions of its muscles directed towards the pharynx (antiperistalsis) throw them into the oral cavity. The nasopharynx and the larynx close, while the tongue is not raised, but is, on the contrary, drawn downward. The mouth opens reflexly.

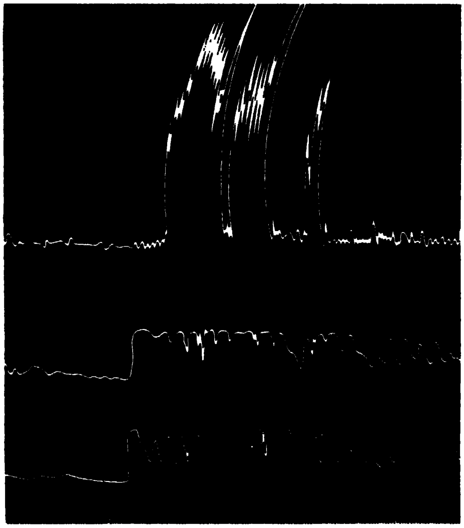

Fig. 118. Curve of vomitive movements. Record of movements of stomach (upper line), duodenum (second line from top), small intestine (third line from top). Lower line marks time (after Y. Babsky).

Vomiting may be caused by stimulation of the receptors of the stomach, the receptors of the base of the tongue, the pharynx, the organs of the abdominal cavity, the internal ear, etc. It is provoked either by a strong mechanical stimulation of the corresponding receptors (for example, strong pressure in the gastric cavity when the stomach is overfilled, tickling of the base of the tongue or of the pharynx, tension in the peritoneum) or by their stimulation with certain chemicals (usually harmful for the organism). Vomiting thus occurs under the action of agents which may hurt the organs of digestion. It also occurs reflexly in various inflammations of the abdominal cavity and of the peritoneum.

In all these cases vomiting is a reflex act. The excitation of the afferent paths is transferred to the efferent in the medulla oblongata (a special "vomiting centre" in the medulla oblongata has been described). Excitation of this centre may also be produced by developing a conditioned reflex as a result of combining any indifferent agent with the action of a stimulus which causes vomiting (Podkopayev, Krylov).

A strong concussion of the brain may cause vomiting movements due to the direct stimulation of the nervous centres. Their excitation can also be produced by the action of certain chemical substances brought by the blood directly to the nerve cells of the vomiting centre. Typical in this respect is the vomiting which follows an injection of apomorphine into the blood or subcutaneously; vomiting ensues several minutes after an injection of this substance, sometimes repeating several times depending upon the fulness of the stomach.

Vomiting begins during expiration. Increased breathing may stop vomiting.

General Review of Gastric Functions

In highly organized animals and in man the functions of digesting and assimilating the nutritive substances are under the control of the central nervous system.

Subjectively we perceive, for example, the excited state of certain divisions of the central nervous system as appetite and during the same, but more sharply pronounced states, we feel hunger.

The secretion of gastric juice in the act of eating and even only in a situation in which there is eating (the latter due to conditioned reflexes developed in response to visual, olfactory and auditory stimuli) is at once a physiological and a "psychic" act—a special qualitative phenomenon experienced subjectively. The physiological process of gastric juice secretion, as well as the motor processes during food consumption and the subjectively experienced phenomenon of appetite are, thus, a single material process.

Pavlov disclosed the physiological nature of this most complex phenomenon and showed it was a complex-reflex process, in which, as was pointed out above, the higher division of the central nervous system—the cerebral cortex—is the first to take part. The laws established by Pavlov have been confirmed by the investigations of a number of physiologists and clinical workers who have studied the development of the conditioned-reflex secretion of gastric juice in man.

Pavlov advanced an important hypothesis of objective interpretation of the entire complex food reaction in higher animals and in man by his theory of a "food centre." By analogy with the respiratory centre the food centre must be conceived as the functional union of all cellular elements in the central nervous system, which receive the stimuli connected with the act of eating and the digestion of food. All these cellular elements are also interconnected with the groups of nerve cells in the different parts of the central nervous system which send efferent impulses to the working, executive organs, the glands and muscles involved in digestion.

The question is: what stimulates this "food centre" with its numerous cell groups? Experience shows that this centre is stimulated, primarily, reflexly and also by the chemical stimuli which are carried by the blood directly to the nerve cells.

The food centre can be stimulated and inhibited, both. Clinical practice shows frequent variations in appetite, which often decreases and is even completely lost. This is always connected with a reduced secretion of gastric juice. The cutting of various nerves, precisely like their chemical paralysis (for example, novocainization), destroys the unity of the complex—the secretion of the glands and the feeling of appetite.

In addition to the external receptor fields in the organs of the mouth, the oesophagus and the stomach there is an enormous number of receptor apparatus, interoceptors, whose excitation also stimulates the food centre. When Pavlov wrote his lectures on the physiology of digestion (1897) he still made use of certain psychological ideas and terms. "It can hardly be doubted," he wrote, "that under normal conditions the stomach is also a seat of certain sensations, i.e., its internal membrane possesses a certain degree of the sense of touch.* We now know definitely that the walls of the stomach contain numerous mechano-, thermo- and chemoreceptors (Bykov, Chernigovsky, Ivanov et al.).

Chemical stimuli in the blood may also directly influence the receptor cellular apparatus in the central nervous system itself. That is why, for example, a protracted monotonous diet, which changes the physicochemical composition of the blood in a certain direction, may, for some time, act as a stimulus to the "food centre."

Changes in the blood chemistry during normal pregnancy may be attended by changes in the excitability of the central nervous system, or new stimuli may appear which excite and alter the excitability of the nervous apparatus. This was confirmed by the study of the secretion of the gastric glands in pregnant dogs.

The whole complex neurohumoral mechanism of the function of gastric glands may also be changed by other excited or inhibited centres so that this function is either increased, depressed or completely inhibited. In this case we observe complex interactions of two antagonistic processes—stimulation and inhibition.

This is particularly true of the complex dynamics of the processes which occur in the cerebral cortex. Various unconditioned or conditioned reflex processes (especially the latter), strongly pronounced or acting on the organism for a long time, may pervert the normal activity of the glandular and motor apparatus of the stomach, or impair this activity by changing the work of the vascular and lymphatic systems.

CHAPTER 27

FUNCTION OF THE PANCREAS

The food that enters the duodenum from the stomach is subjected to the action of digestive juices. Bile and the pancreatic and intestinal juices are discharged into the duodenum.

Structure of the Pancreas

The pancreas is one of the most important digestive glands. It is located alongside the duodenum and two of its ducts (in man and in some animals, for example, in dogs) and sometimes several additional ducts empty their secretion into the duodenum.

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* I. Pavlov, *Complete Works*, Vol. II, Book 2, p. 124.

Microscopically the pancreas consists of two types of cells: some secrete pancreatic digestive juice, others—the cells of the so-called islands of Langerhans—secrete a hormone called insulin (p. 424).

Each cell secreting pancreatic juice consists of two layers: the outer, nearly homogeneous, adjoining the *membrana propria,* and the inner, granular, lying next to the alveolar lumen. The nucleus lies on the border of these layers. When the gland is inactive the granular layer occupies the greater part of the cell. During secretion the granular layer gradually diminishes, reverting to the original state after secretion. Cutting the nerves which innervate the gland slows down the process of granule accumulation in its cells, and owing to this the granules are washed out faster in the denervated gland than normally.

The pancreas is abundantly supplied with nerves. It is innervated by the vagus and the sympathetic nerves; the glandular cells and the islands of Langerhans are innervated separately.

The branches of the nerves innervating the pancreas anastomose with the branches innervating the adjacent organs. Because of this it is possible to speak of common innervation of the stomach, the duodenum, the pancreas and the liver with its accessory organs.

The receptor apparatus of the pancreas is likewise highly developed; this has been shown in experiments with stimulation of its receptors (Alexeyev) and in morphological studies (Godinov).

The ducts of the gland contain bundles of smooth muscle fibres; when these fibres contract, the secretion (and the production of the secretion) may slow down or temporarily cease completely. The blood and lymph supply of the gland is ensured by a large number of blood and lymph vessels. During the secretion of pancreatic juice the amount of blood running through the gland sharply increases.

Collection of Pancreatic Juice

Pancreatic juice may be obtained in two ways: in an *acute* experiment, in which the juice is collected from a canula inserted into the duct of the gland after opening the abdominal cavity, and in a *chronic* experiment—from the pancreatic duct brought to the exterior of the abdominal wall. Attempts to use the latter method had been made for a long time, but they were crowned with success only in the hands of the great experimenter —Pavlov, who developed a method of collecting pancreatic juice for a long time from a normal animal completely recovered from the operation.

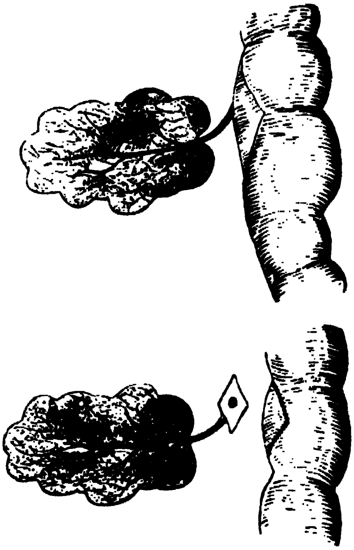

Fig. 119. Diagram of operation for creating pancreatic fistula. Top—papilla of duct is separated from duodenum; bottom—papilla drawn to skin surface (after I. Pavlov).

Pavlov's method consists in the following: a small piece of mucous membrane of the intestine is excised together with the duct opening into it; the intestine is sewn up, while the excised section together with the orifice of the duct is brought to the exterior and grafted to the abdominal skin (Fig. 119). The dog, thus operated, secretes part of the juice, produced by the gland, to the exterior, while the other part of the juice enters the duodenum through the other duct still connected with the intestine. If the dog is properly cared for and big losses of the juice are prevented, the animal can keep well for a very long time.

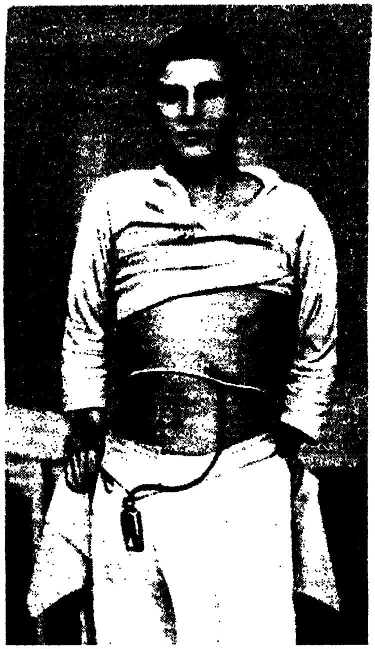

Fig. 120. Chronic pancreatic fistula in man formed as result of accidental injury.

Human pancreatic juice is obtained in clinics through a tube inserted into the duodenum, but the liquid pumped out is mixed with other secretions which pour into the intestine. Several cases of observation of people who had pancreatic fistulas have been described. For example, a patient, who secreted pure pancreatic juice through a fistula (Fig. 120) was kept under observation in 1935 (Bykov and Davydov).

Composition and Secretion of Pancreatic Juice

Pure pancreatic juice is a clear colourless liquid of an alkaline reaction whose pH varies within the limits of 7.8 to 8.4.

The solids consist of organic and inorganic substances. Proteins form the main part of the organic substances; in addition, there is always an admixture of mucous substances sometimes visible to the naked eye and sometimes dissolved and observed only after precipitation; the mucous substances are partly secreted by the glandules of the duct itself. Of the inorganic solids sodium bicarbonate, which is responsible for the alkaline reaction of the juice, is the most important.

The pancreatic juice secreted by the dog in 24 hours contains about 10 gr. of proteins. The secretion of a large amount of sodium bicarbonate with the juice brings alkaline substances to the intestine. When the juice is brought to the exterior the acid-base balance of the body alters; the pancreas undoubtedly influences the state of this balance. If the animal with a pancreatic fistula is given soda the normal acid-base balance may be maintained.

Pancreatic juice contains enzymes which act on proteins, fats and carbohydrates. *Trypsin,* a proteolytic enzyme, acts on proteins, *lipase* or *steapsin,* a lipolytic enzyme, acts on fats, and *amylase,* an amylolytic enzyme, acts on carbohydrates.

What was formerly called trypsin turned out to be a complex of proteolytic enzymes consisting of trypsin proper, chemotrypsin and carboxypeptidase. Because of this the pancreatic juice extensively hydrolyzes proteins. Unlike pepsin it does not convert proteins into peptones, but into their end products ready for absorption, i.e., amino acids.

Trypsin acts in a mildly alkaline, neutral or mildly acid medium. The juice collected—*without* contact with the intestinal papilla—directly from the duct of a chronic pancreatic fistula of the dog contains trypsin in an inactive state, the so-called *trypsinogen*. In order that trypsinogen, the inactive enzyme produced by the cells of the gland, become active it requires the influence of a special enzyme—*enterokinase*, contained in the *intestinal juice* (this enzyme, which activates another enzyme, i.e., an enzyme of an enzyme, discovered in Pavlov's laboratory, was the first of the substances of analogous action which have become known and which have acquired the generic name of *kinases*). A negligible dose of enterokinase, contained in a very small amount of intestinal juice, suffices to activate large amounts of trypsinogen. The activation of the protein enzyme of the pancreatic juice takes place, therefore, immediately upon its contact with the wall of the duodenum at the point of the duct's entrance. If the pancreatic juice contains a very large amount of the protein enzyme, part of it turns out to be active. In this case its action is augmented by activation.

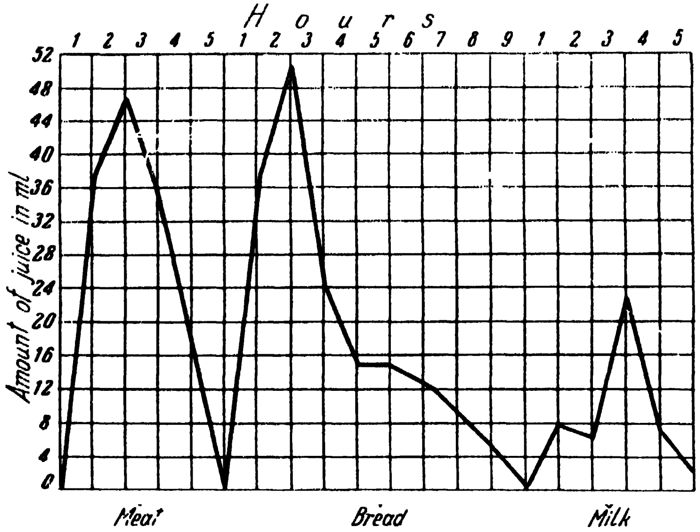

Fig. 121. Secretion of pancreatic juice in the dog by the hour when eating meat, bread and milk (after A. Walther).

To determine the action of trypsin Mett's method or titration with formol of the amide groups, produced by protein conversion, may be used.

Lipase, the fat enzyme of the pancreatic juice, splits up neutral fat into glycerine and fatty acids; the fatty acids form soaps with the juice alkalis. Lipase, like trypsin, is secreted by the cells of the pancreas in an absolutely or nearly absolutely inactive state. ***Lipase is activated by the bile salts contained in the bile.*** The addition of intestinal juice to the pancreatic juice augments the action of lipase. The pancreatic juice and bile also aid in *emulsifying* fats. The action of lipase, which splits up fats, may be measured quantitatively by titration of the fatty acids formed from the fat with an alkali.

Amylase is secreted by the pancreas in an active form and acts vigorously on starch changing it through a series of dextrins to maltose; maltose is converted by maltase into glucose.

Pancreatic juice also contains rennin, maltase, lactase, nuclease (which splits up complex proteins—nucleins) and a very small amount of erepsin, an enzyme which splits up albumoses and peptones, but not proteins as such, into amino acids.

Periodicity of secretion. Pancreatic juice is not secreted on an empty stomach or in the absence of special stimuli connected with eating. Only during the periodic "work" of the gastrointestinal tract in a hungry state (p. 299) is some pancreatic juice secreted. Abundant secretion of the juice starts within 2 to 3 minutes after the beginning of eating, then it slows down for a while, but several minutes later begins to increase again. This increase continues for a few hours. It can be observed in dogs with chronic fistulas or in patients with the pancreatic juice secreted to the exterior that a definite amount of juice is secreted for each kind of food, that the secretion is of a characteristic duration and nature and that it produces juice of a certain quality. The course of juice secretion is shown in Fig. 121.

Observations show that the greatest amount of juice in man, as well as in dogs, is secreted after carbohydrate food, less after meat food and least of all after fats (Table 11). The pancreas of man secretes 1,500 to 2,000 ml. of juice in 24 hours.

Table 11

Secretion of Pancreatic Juice (in ml.) in Man after Eating Meat, Bread and Milk

(by the hour)

Hours after food intake	Amount of juice after intake of		
	Meat 200 gr.	Bread 400 gr. and glass of tea	Milk 600 ml.
1	5.0	7.8	4.0
2	5.2	5.2	4.0
3	4.2	3.2	3.0
4	2.1	3.4	4.5
Total	16.5	19.6	15.5

Long-continued consumption of food rich in fats causes the secretion of juice gradually to diminish. This is shown in Table 12.

Table 12

Pancreatic Secretion (in ml.) in a Fat Diet Continued for 5 Days

Period of juice secretion	1st 24 hrs.	2nd 24 hrs.	3rd 24 hrs.	4th 24 hrs.	5th 24 hrs.
During the day......	90.5	88.0	80.8	52.5	36.0
During the night	16.0	1.9	2.0	6.0	3.0
Total for 24 hours ...	106.5	89.9	82.8		

The comparison of the curves of pancreatic and gastric juice secretion, when the same foodstuffs are consumed, reveals a great likeness of the curves; this alone points to an interrelation in the work of the stomach and the pancreas. The given interrelation is conditioned, as we shall later see, by the common secreting mechanisms and by the influence of the gastric juice on the activity of the pancreas.

Nervous Regulation of Pancreatic Secretion

Pavlov convincingly proved both in acute experiments and on animals with a chronic fistula that stimulation of the vagi caused pancreatic secretion. Taking into consideration the failures of the former investigations which were due to the extreme sensitivity of the gland to any disorder in circulation, to pain stimuli and to anaesthesia, Pavlov reduced to the minimum the stimuli occurring in acute experiments and by stimulating the distal end of the severed vagus under these conditions discovered its stimulating action on the pancreas.

Pavlov showed the same thing by stimulating the distal end of the vagus cut in the neck 3 to 4 days before the experiment. In this case the vasoconstrictor and secretion-inhibiting fibres of the vagi have time to degenerate, while the secretory fibres being more resistant, maintain their efficiency and, when stimulated, cause the pancreas to secrete.

This experiment was later reproduced by A. Tonkikh and other investigators under particularly strict experimental conditions excluding the possibility of pancreatic secretion under the influence of the passage of gastric juice into the intestine, which is also secreted when the vagi are stimulated (see p. 261).

Two to three minutes pass from the time the vagus is stimulated to the beginning of the secretion with an aftereffect observed at the end of the stimulation. Repeated stimulation yields a more abundant secretion which begins after a shorter latent period. Because of this Pavlov assumed that the vagi carried fibres capable not only of stimulating but also of inhibiting the secretion.

Pancreatic juice secretion after stimulation of the vagus is always scant, but the secreted juice is richer in organic substances (7 to 8 per cent) and enzymes. The action of the vagi on the secretion of the pancreas generally resembles that of the sympathetic nerves on the secretion of the salivary glands. Razenkov suggests that the vagus does not have so much to do with the secretion of the pancreatic juice as with the accumulation and disintegration of the granules in the secretory material of the gland.

Stimulation of the sympathetic nerve also causes the pancreas to secrete juice.

The action of the secretory fibres on the pancreas is also revealed in the experiments with sham feeding conducted on dogs with a chronic pancreatic fistula. Under these conditions the secretion of pancreatic juice begins much *earlier* than the secretion of gastric juice. The pancreas starts secreting already 2 or 3 minutes after the beginning of sham feeding. Bykov and Davydov observed the secretion of pancreatic juice in a man with a pancreatic fistula 2 to 3 minutes after they had talked to him about eating or showed him a tasty dish. Hence, conditioned-reflex secretion of pancreatic juice in man was proved. These experiments show that *pancreatic juice secretion during the first minutes after feeding is conditioned by a reflex mechanism.* The reflex impulses arise under the action of food stimuli on the same receptors whose stimulation causes all food reflexes. In the brain stem the afferent impulses switch over to the fibres of the vagi and the sympathetic nerves which innervate the pancreas.

The other and more intricate mechanism of pancreatic juice secretion is the neurohumoral. It was ascertained in Pavlov's laboratory a long time ago that a lot of pancreatic juice is secreted when *gastric juice* or *hydrochloric acid* are poured into the duodenum.

This phenomenon was formerly explained by the fact that by stimulating the sensitive endings located in the intestine hydrochloric acid caused the pancreas to secrete juice reflexly. The study of the mechanism of the action of hydrochloric acid on pancreatic secretion was continued by Bayliss and Starling, British physiologists, who showed in 1902 that the pancreas secreted normally even when hydrochloric acid was poured into an isolated portion of the intestine which had retained its normal blood supply. Injected directly into the blood, hydrochloric acid causes no secretion of pancreatic juice. Hence the idea that under the action of the acid on the wall of the intestine it forms a special substance, which is absorbed and carried by the blood to the glandular apparatus of the pancreas where it stimulates secretion. The correctness of this view was proved by the fact that it is easy to prepare an extract of the mucous membrane of the intestine with a weak solution of HCl which causes an abundant secretion of the pancreas when injected into the blood.

The conclusion was made that abundant juice secretion, when hydrochloric acid and gastric juice, as well as fatty acids and certain other compounds enter the intestine, is due to the fact that under the action of these agents on the wall of the intestine a special substance—*secretin*—passes from the wall of the intestine into the blood. Secretin, a polypeptide produced in the mucous membrane of the intestine and carried by the blood to the cells of the pancreas, acts on them as a stimulus. By its physiological action secretin is a hormone,* i.e., a substance which is formed in a *certain* organ, is carried from it by the *blood* through the body and acts selectively only on a certain organ or on a number of organs.

If there are no acid or such stimulants of pancreatic secretion as soaps and fatty acids, the pancreas does not secrete any juice and, hence, no secretin enters the blood. And, since an abundant secretion of the pancreas begins when HCl (and certain other substances) enter the intestine, it must be assumed that these stimulants of the secretion either ensure the formation of secretin in the wall of the intestine or in some way condition its passage into the blood.

Secretin has now been obtained in crystal form; it is also possible to obtain its chloride. The molecular weight of secretin is approximately 5,000. Under the influence of certain substances, such as alcohol, alkalis and acids in a certain concentration, crystal secretin becomes inactive. By its physiological nature secretin is a substance which acts selectively on the pancreas, when injected into the blood, and is inert when injected subcutaneously or intramuscularly.

According to the investigations of some authors the effect of secretin does not diminish with the denervation of the pancreas and introduction of atropine into the blood, since atropine eliminates the effect of excitation of the parasympathetic fibres. True, it must be observed that it is hardly possible completely to denervate such an organ as the pancreas, which receives an enormous number of nervous branches from various sources.

When the vagi or the sympathetic nerves are stimulated the secretion is less abundant than when it is caused by secretin, but in the latter case the juice contains less protein and enzymes. An assumption has been made that the content of solid organic constituents of pancreatic juice is regulated by the vagus, while the secretion of the liquid part and the content of salts is regulated by secretin. This assumption of a division of a single complex process taking place in the same cellular structures cannot be accepted since it is based on a narrow analytical approach to a physiological process and on data obtained mainly in an acute experiment under artificial conditions. Extensive experimental material shows that the normal secretion is conditioned by a combination of both mechanisms—the nervous and the humoral.

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* It was in connection with the discovery of secretin that Starling introduced the term "hormone" into physiology.

It must be borne in mind, firstly, that the reflex arc involves the humoral link and, secondly, that a chemical or any other stimulus acts on the secretory cell through the nervous apparatus and involves the chemical transmitters of the stimulation.

Of great interest in this respect are Solovyov's experiments repeated in the laboratory headed by K. Koshtoyants. These investigations, conducted on animals operated on by Pavlov's method, necessitate a reconsideration of the humoral theory of Bayliss and Starling. Pavlov always pointed out that the nervous system was the main source of stimulation of the pancreas. Solovyov showed that switching off the sympathetic nervous system by ergotoxin almost completely depressed the secretion begun in response to the introduction of acid into the duodenum. It follows that the secretin, formed in the intestine and brought by the blood to the pancreas, acts on the secretory apparatus of the gland through the nervous system. The humoral mechanism is, thus, not independent or isolated, but is included in the single synergically acting complex neurohumoral regulation.

Secretion of Pancreatic Juice after Ingestion of Fat

Of the substances, which upon entering the intestine cause an abundant secretion of pancreatic juice, special mention, besides HCl, should be made of fat; the latter, as we saw it, inhibits the secretion of gastric juice.

An alkaline reaction in the duodenum may continue for a long time after consumption of fatty food. Despite this the passage of fat into the duodenum causes an abundant secretion of pancreatic juice. The mechanism of this juice secretion is not quite clear as yet. No doubt the fatty acids and soaps, and, probably, neutral fat lead, like the acids, to secretin production. At the same time the pancreatic juice secreted when fat is introduced into the intestine is much richer in solids and enzymes than the juice secreted after ingestion of acid. If we paralyze with atropine the effect produced by stimulation of the parasympathetic nerves the composition of the juice secreted after ingestion of fat will be the same as the one secreted after acid.

It is, therefore, probable that fat and fatty acids act on the pancreatic secretion in two ways: they stimulate the gland humorally due to the formation of secretin and at the same time by stimulating the receptors of the intestine (or, according to Tonkikh's data, even the pylorus) they act on the pancreas reflexly with the reflex influence particularly manifest in the *nature* of the pancreatic secretion.

Mechanism of Pancreatic Secretion after Ingestion of Various Foodstuffs

Pancreatic secretion begins soon after eating because it is conditioned by a reflex from the oral cavity transmitted to the pancreas mainly through the vagus. But most important in the total picture of juice secretion is the stimulating action of the secretin formed in the wall of the intestine when the hydrochloric acid of the gastric juice enters the intestine. That is why the curves of pancreatic secretion repeat somewhat tardily, as it were, the curve of gastric secretion.

With the cessation of gastric secretion no more acid passes into the intestine and, hence, there is no secretion of secretin into the blood and no secretion of pancreatic juice. For example, secretion of gastric juice after eating bread diminishes beginning with the second or third hour, and at the same time a diminution of the pancreatic secretion is observed. In addition, the gastric secretion after eating bread is long maintained on a low level (8 to 10 hours) and this is also repeated in the curve reflecting the pancreatic secretion after eating bread. Gastric secretion after eating meat ends, as is well known, sooner than after eating bread; we observe the same as regards pancreatic juice secretion. Besides, it is not only the duration of the secretion, but also the total amount of the secreted juice that is greater after bread than meat eating. The latter is due to the fact that the proteins of the meat neutralize the HCl of the gastric juice more than do the bread proteins, owing to which the gastric contents, which pass into the intestine when bread is eaten, have a stronger acid reaction than when meat is consumed, and a more acid reaction of the gastric contents causes the pancreas to secrete a larger amount of juice.

Secretion of pancreatic juice after drinking milk is conditioned partly by the passage of acid into the intestine secreted on the milk in the stomach, and partly by the above-considered juice-stimulating ("secretin-nervous") action of fats on the secretion of the pancreas. The fatter the food and, hence, the greater the inhibition of gastric juice secretion, the greater the importance of the mechanism of the stimulating action of the fats.

The enormous significance of hydrochloric acid secreted in the stomach as an agent which stimulates the secretion of the pancreas, makes it clear why digestion in the intestine is also impaired when the acidity of the gastric juice is reduced (achylia).

It should be noted here that secretin is also formed when water is introduced into the stomach (especially carbonated [CO_2] water, or water acidified by some organic acids contained in fruits and vegetables).

Cranberry and lemon juices cause vigorous pancreatic secretion. It is probable that other juices of fruits and berries also act similarly when introduced in certain concentrations into the stomach or directly into the intestine. On the contrary, whole, undissolved vegetable juices depress the secretion of the pancreas (Leporsky and his associates).

CHAPTER 28

SECRETION AND EXCRETION OF BILE

Bile and intestinal juice act on food in close association with pancreatic juice.

Bile is produced in the liver *incessantly*; this is due to the fact that bile production is not only a secretory process, but excretory as well (excretion of bile pigments and other substances); production of bile already begins in the six-month-old embryo with the products of the iron-containing part of haemoglobin transformed into bile pigments.

Bile production may sharply decrease (but not discontinue) only in case of protracted starvation.

The amount of bile secreted in 24 hours varies rather widely, constituting 800 to 1,000 ml. in human adults.

While bile is produced uninterruptedly its *passage* into the intestine is connected with the entrance of food into the alimentary canal. The continuously produced bile passes into the bile ducts and the gallbladder. It is evacuated into the duodenum through the common bile duct. The topographic relations of this duct to the liver, the gallbladder, the hepatic ducts and the cystic duct are shown in Fig. 122.

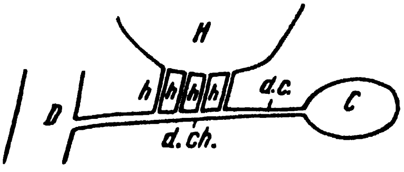

Fig. 122. Diagram of bile ducts.
D—duodenum; *H*—liver; *C*—gallbladder; *h*—hepatic duct; *d.c.*—cystic duct; *d.ch.*—common bile duct.

The human gallbladder has a layer of muscles consisting of longitudinal and circular fibres. The thickness of the muscular layer depends on the number of muscle bundles. A thickening of the circular layer is observed in the neck of the bladder whence the muscle fibres pass into the walls of the cystic duct and Heister's valves. The hepatic and cystic ducts have no muscle fibres. In the common duct the muscle fibres are weakly developed except in its distal end; the distal end of the common bile duct is considerably strengthened by the musculature of the duodenum at its entrance into the intestinal wall. At the mouth of the duct, in the *papilla Vateri*, there is a circular locking muscle—the *sphincter of Oddi*, separated from the intestinal wall by connective tissue and connected with it by thin muscle fibres.

After bile passes from the liver into the bladder it concentrates four- to tenfold due to the absorption of the water from the gallbladder into the blood. At this time some of the substances dissolved in the bile are also absorbed into the blood. Because of the condensation of the bile the bladder can hold ever new portions of it flowing in from the liver.

The absorption of water from the bladder is also significant for the equalization of pressure throughout the bile-secreting system.

Composition and Role of Bile

Owing to the fact that bile can run from the liver either directly into the intestine or first into the gallbladder the intestine sometimes receives bile which had for some time accumulated in the bladder—the so-called *gallbladder bile,* and sometimes the bile excreted directly by the liver—*liver bile.* Since gallbladder bile is strongly concentrated it is of much darker colour than the liver bile.

The constituents of bile are bile acids, bile pigments, cholesterol, lecithin, mucin and inorganic compounds (salts of sodium, potassium, magnesium, calcium, etc.). Various acids have been extracted from the bile of different animals; representatives of two groups of bile acids are most frequently encountered in the human bile—glycocholic and taurocholic acids.

Investigations in the laboratory headed by Razenkov (the investigations were conducted by the tracer atom method) have shown that phosphorus is secreted with bile in much larger quantities than with the other digestive juices; the presence of phosphorus compounds in the bile is connected with metabolic processes. The excretion of phosphorus from the organism is, thus, in large measure connected with the liver.

The colour of bile depends on two colouring substances (pigments) it contains: bilirubin and biliverdin. The colouring of the bile changes according to whether the golden-yellow bilirubin, or the product of its oxidation—biliverdin—prevails. The bile of herbivores is dark green, of carnivores—reddish-yellow. Bilirubin is more widespread since it is a product of transformation of the haemoglobin of the destroyed erythrocytes. The pigments of the urine and faeces—urobilinogen and stercobilinogen—are formed from the bile pigments.

The role of bile in the digestive process consists in the following: 1) its acids activate the lipase of the pancreatic juice and augment the action of its proteolytic and aminolytic enzymes; 2) it is capable of dissolving a large amount of fatty acids; 3) it aids considerably in maintaining the fats in an emulsified state, due to the reduced surface tension, the emulsification of the fats making their particles accessible to the action of lipase; it thus holds in solution and brings in close mutual contact fats, fatty acids and the lipolytic enzyme; 4) bile is necessary for the absorption of the products of fat digestion; 5) along with other digestive juices it neutralizes the acid chyme which enters the intestine from the stomach, in connection with which the action of pepsin ceases. It thus prevents the destruction of trypsin by pepsin. Even with the acid reaction of the intestinal contents bile precipitates the proteins, draws the pepsin away and thus puts an end to peptic digestion creating more favourable conditions for tryptic digestion.

The bile of man and some animals contains a proteolytic and a diastatic enzymes, but their action is very weak. It is also believed that bile influences intestinal movements.

Methods Used in Studying Bile Secretion and Bile Excretion

A permanent fistula of the gallbladder is used for the study of bile secretion. When the fistula is open, practically the entire bile secreted by the liver flows out through the bladder. If the *excretion of bile into the intestine* is to be studied a permanent fistula is created in the bile duct by Pavlov's method. This method essentially consists in the following: a piece of intestine is excised at the point where the common duct opens; this piece with the orifice of the duct is engrafted into the abdominal wound while the intestine is sutured.

In Pavlov's laboratory Volborth proposed to fistulize simultaneously the gallbladder and the bile duct to observe the secretion of the bile and its liberation into the intestine.

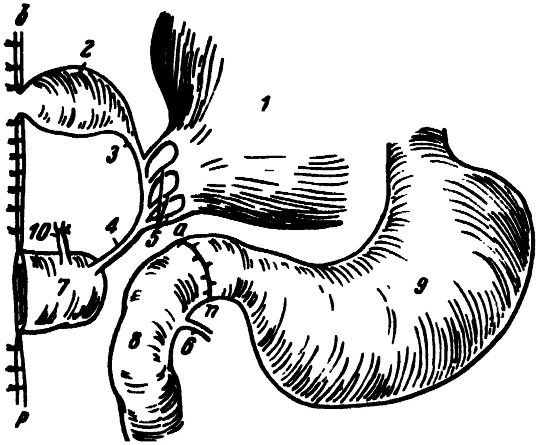

Fig. 123. Diagram of operation for creating common bile duct fistula (after S. Gorshkova and G. Inasaridze).

1 liver; *2* gallbladder; *3* -cystic duct; *4* common bile duct; *5*— hepatic ducts; *6*—large pancreatic duct; *7*—isolated portion of duodenum; *8*—duodenum; *9*—stomach; *10* ligated small pancreatic duct; *a-n* anastomosis; *b-p*—stitches on abdominal wound.

The recently developed method of fistulizing the gallbladder and the duct makes it possible to avoid the obstruction to the outflow of the bile due to the scars formed by the use of the above-mentioned methods. The operation consists in the following: a small portion of the duodenum, excised together with the opening of the bile duct, is sutured on one side and into the skin wound on the other side (operation of the Thiry type, Fig. 123); the integrity of the intestine is restored. Some time later a fistula is created in the gallbladder of the same animal. This method of operation eliminates the kinking and stretch of the bile duct and completely excludes the mechanical obstructions by scars which compress the duct at the point of its entrance into the intestine. In addition, the operation makes it possible to retain the normal work of the sphincter of Oddi and of the intramural mechanism which is of great importance for the evacuation of the bile.

Secretion of Bile by the Liver

Production of bile is, as was stated above, an incessant process, which can, however, be intensified by the action of different agents called cholagogues. *This increase of bile secretion* is *observed* under the *following* conditions:

1) when bile acids or bile are introduced into the body (into the blood or into the digestive tract). It is probable that these substances, excreted through the liver, stimulate the neuroglandular apparatus of the liver while circulating in the blood;

2) when hydrochloric acid of the gastric juice, acid liquids (for example, juices of berries and fruits), egg-yolks, mineral waters and, to a lesser extent, water enter the intestine. It is not improbable, though it has not yet been definitely proved, that the increased bile secretion caused by the action of these agents on the walls of the intestine, is due to the liberation of secretin into the blood (p. 280);

3) when the mechanoreceptors of the stomach are stimulated, which warrants the assumption that an unconditioned-reflex increase in bile secretion is possible in response to the filling of the stomach with food.

Secretion of bile may be intensified not only under the influence of the above-mentioned agents, but also by any stimulus used simultaneously with cholagogues. In other words, stimulation of bile production may involve the cerebral cortex due to the development of a conditioned reflex (Rickl, Ivanov et al.).

The bile secreted by the liver flows down the ducts into the gallbladder and if the pressure in the latter does not reach a certain value it does not enter the intestine, but concentrates in the bladder.

Contractions of the Gallbladder

Outside the periods of digestion the muscles of the gallbladder are relaxed with only rhythmic contractions sometimes observed. Strong contractions of the gallbladder (Fig. 124) are provoked, firstly, by the intake of food in the act of eating (and owing to the development of a conditioned reflex by all the attending stimuli connected with eating) and, secondly, by certain agents, which stimulate the muscles of the gallbladder from the intestine. The agents, which cause the bladder to contract, are: 1) yolks, 2) fat and milk, and 3) products of protein digestion—peptones. Some substances, which sharply increase the secretion of bile by the liver, such as HCl, bile and water, lead to a relaxation of the gallbladder wall.

The rhythmic contractions of the gallbladder, once begun under the influence of stimuli which entered the intestine, continue for a long time

(3 to 4 hours and longer), gradually fading. The degree of tension of the bladder alters along with the rhythmic contractions, i.e., its tonus alters; higher tonus is usually attended by an intensification of contractions.

The movements of the gallbladder are essentially determined by nervous influences and are stimulated by fibres of the vagus which are the motor fibres for the muscles of the gallbladder. Paralysis of the stimulatory effect of the parasympathetic fibres under the action of atropine diminishes the contractions of the bladder, while stimulation of the endings of the vagi with pilocarpine, as well as the injection of choline and acetylcholine, sharply increases these contractions. Sympathetic fibres, which inhibit the muscles of the gallbladder, run in the splanchnic nerve. As usual, adrenalin exerts the same influence as the sympathetic nerve: it inhibits the movements of the gallbladder.

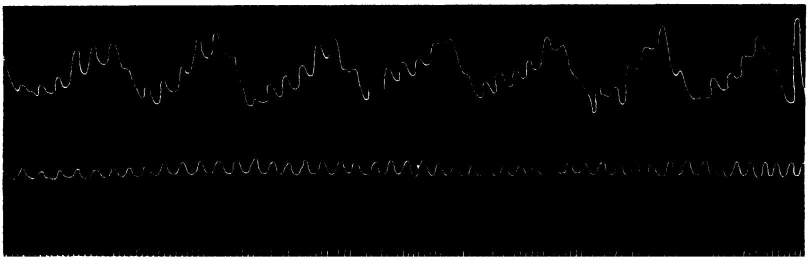

Fig. 124. Rhythmic contractions of gallbladder (upper record); record of breathing (middle line); lower line marks time (1 second).

It is very probable that under normal conditions the distention of the gallbladder by stimulating the interoceptors reflexly produces its own contraction. The wall of the gallbladder is also extraordinarily rich in receptor nerve endings whose stimulation, if sufficiently strong, causes acute pain.

There are, apparently, also humoral influences on the muscles of the gallbladder. A special hormone—*cholecystokinin*— has been described; this hormone is liberated in the wall of the intestine under the same conditions as secretin and stimulates the movements of the gallbladder through the blood.

Passage of Bile into the Intestine

The passage of bile into the intestine depends on its secretion by the *liver* and on its *ejection from the gallbladder* by the contractions of the latter's walls. Outside digestion the bile enters the intestine in negligible amounts only during the so-called periodic activity of the digestive apparatus.

It has been found that bile can be secreted into the intestine only when the pressure in the bile-secreting system reaches a certain value. If there is little bile in this system in the beginning of eating its pressure is negligible and 20 to 30 minutes pass from the moment of eating to the time the bile enters the intestine. There is usually always some bile in the gallbladder and it begins to flow into the intestine approximately 8 minutes after consumption of meat, 12 minutes after eating bread and 3 minutes after drinking milk. If the bile-secreting system be filled artificially the latent period of the bile's passage into the intestine can be shortened even more. Once begun, the flow of bile into the intestine continues for 5 to 7 hours after consumption of milk or meat and for 8 to 9 hours after eating bread. The total amount of bile secreted in response to these stimuli, however, is nearly the same; though the secretion following ingestion of meat and milk is of a briefer duration, it is more intensive.

The process of normal digestion involves a coordination of factors, which influence the secretion of bile by the liver and the movements of the gallbladder and the ducts. The HCl of the gastric juice, egg-yolk, water and bile itself, reabsorbed from the intestine, stimulate the *secretion* of bile. Because of this the bile-secreting system is filled to a greater extent with the HCl, bile and water, simultaneously leading to a *relaxation of the gallbladder*. At the same time the act of eating, the fats, egg-yolk and the products of protein digestion stimulate the *contractions* of the bladder. The coordination of these stimuli may create the most diverse conditions for the passage of the bile into the intestine. After consumption of fats and egg-yolk the gallbladder may be entirely free of bile by the time the bile enters the intestine. In other cases, especially when large amounts of the acid contents of the stomach enter the intestine, certain quantities of bile may pass into the gallbladder even before the intensified secretion of bile by the liver has ended.

The condition of the duct muscles and, especially, the sphincter of Oddi is undoubtedly important during the passage of bile into the intestine. Impulses from the vagus relax this sphincter, while the impulses from the sympathetic nerve increase its tonus (the opposite holds true for the gallbladder). The bladder, probably, contracts at the same time as the sphincter of Oddi relaxes. The correlation between the production of bile in the liver and its liberation into the intestine is very complex and has not yet been sufficiently studied.

The content of solid constituents in the bile depends mainly on how long the bile entering the intestine was retained in the biliary passages. The longer bile remains in the bladder, the more concentrated it is; but the composition of liver bile also varies with the conditions which cause its secretion.

Comparing the curves of the passage of bile into the intestine with the curves of the passage of pancreatic juice we can observe that in most cases the secretion of bile and pancreatic juice is synchronous. The significance of this relationship consists in creating the conditions for the digestion and absorption of fats, which necessarily require the passage of bile into the intestine.

CHAPTER 29

DIGESTION IN THE SMALL AND LARGE INTESTINES

The food already partly digested in the stomach and in the duodenum, i.e., the *chyme,* enters the small intestine, where it is further digested, and thence the large intestine.

The inner surface of the small intestine is lined with villi, most of which are located in its upper segments. Glands of Lieberkühn, which are tubular depressions, open among the villi. Goblet cells, which produce mucus, are located in between these glands. There are special secretory cells of Paneth at the bottom of the glands of Lieberkühn. Lymphatic tissue in the intestinal canal is found in the form of nodular aggregates called Peyer's patches.

Intestinal Juice

Collection of the juice of the small intestine, and its composition. The glands of the small intestine produce intestinal juice which can be collected in a chronic experiment from operated animals. In addition, the juice can be collected from people with fistulas made for therapeutic purposes.

The most convenient method of producing intestinal fistulas in animals is the method of Thiry-Vella. This method consists in the following: a portion of the intestine 30 to 40 cm. long is excised while the mesentery of an intestinal segment is retained (Fig. 125). Both ends of the excised intestinal loop are sewed into the skin wound, whereas the proximal and distal ends of the severed intestine are sutured in order to restore the integrity of the digestive tract.

The intestinal juice secreted through the fistula is composed of two parts: a denser part, containing clumps of mucus, and a more fluid part. The juice has a peculiar odour. Under the microscope the clumps show mucus, cells of the intestinal epithelium and cholesterol crystals. The liquid part is opalescent and has an alkaline reaction.

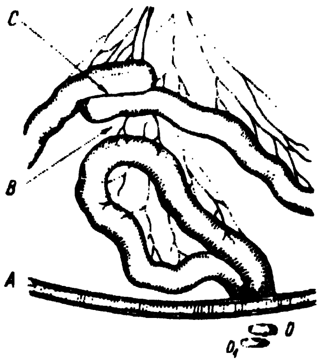

Fig. 125. Chronic intestinal fistula, (after Thiry-Vella).

O and O_1—ends of severed intestine sewn into abdominal wall; A—skin of abdominal wall; B—mesentery with vessels feeding the intestine; C—side to side entero anastomosis (after Egolinsky).

The intestinal juice contains the following enzymes:

1) *erepsin*—a complex of proteolytic enzymes which converts albumoses and peptones into amino acids, while of the proteins they split up only casein; the significance of erepsin consists in the fact that it ends the conversion of the food proteins begun by pepsin and typsin;

2) *enterokinase*, the enzyme of enzymes. discovered in Pavlov's laboratory. Enterokinase activates trypsinogen. More enterokinase is secreted in the upper portions of the intestine than in the lower;

3) *nuclease*—an enzyme which converts nucleins—complex proteins;

4) *lipase* of the intestinal juice which is not a strong enzyme, but is very stable;

5) *enzymes*, which split up carbohydrates, especially disaccharides—*invertase, lactase* and *maltase*.

Secretion of intestinal juice. The intestinal juice of the small intestine is secreted in rather large amounts. Nearly two litres of it is secreted in man in 24 hours. The juice is not secreted incessantly but in connection with the action of stimuli, primarily, under the influence of the mechanical stimulation of the intestinal wall by the denser parts of the chyme. Vigorous juice secretion can be observed in animals with the Thiry-Vella fistula when a drain tube is inserted into the opening of the intestinal fistula. Mechanical stimulation also causes the intestine of man to secrete.

In addition to mechanical stimulation, the secretion of intestinal juice is also caused by chemical substances, namely, gastric juice, spices, acid solutions, soaps, products of protein conversion, lactose, ether, calomel and other substances.

The juice secreted under the action of chemical stimuli, especially mustard oil and hydrochloric acid, contains much liquid and little mucus. Mucus discharges not only a protective function, as it is believed, but is also of importance for the digestion of nutritive materials since it absorbs enzymes and other active substances and transfers them to the substratum (Brestkin and Bykov, Rickl).

When fat food is eaten the amount of intestinal juice secreted in dogs is considerably increased (Shepovalnikov).

The composition of intestinal juice varies with different stimuli. It is known that the contact of pancreatic juice with the wall of the intestine increases the secretion of enterokinase; the entrance of starchy substances increases the amount of amylase in the intestinal juice, while the entrance of fats stimulates the secretion of juice rich in lipase.

Mechanism of secretion of intestinal juice. The effect of the mechanical and chemical stimuli on the intestinal glands is principally due to the local influence of these agents on the neuroglandular apparatus of the intestine. This is clear from the fact that mechanical stimulation of one intestinal segment, which causes intensified secretion of intestinal juice, hardly affects the secretion of the segments removed from the point of stimulation. Cutting the fibres which run to the intestine, i.e., decentralization, disconnection of the intestine from the nerve centres and the ganglionic structures of the abdominal cavity also exerts but little influence on the secretion of intestinal juice, increasing it only slightly.

However, there are also central nervous influences on the secretion of intestinal juice. V. Savich assumed the existence of nervous influences inhibiting the secretion of the intestine. This is confirmed by a certain increase in the secretion of intestinal juice observed after denervation of the intestinal loop. True, hypersecretion may also be due to hyperaemia of the intestine, its increased blood supply after denervation.

The activity of the intestinal glands is regulated by certain humoral agents. Extracts from different organs, particularly the extract from the wall of the intestine, increases production of intestinal juice. The intestinal juice itself, injected into the blood, stimulates the secretion of the glands of Lieberkühn. Some investigators mention the existence of a special hormone (villikinin) which acts on the villi.

On the basis of the modern ideas of regulation of all processes occurring in the internal organs it must be assumed that the regulation of the secretion of intestinal juice, like the regulation of the secretion of other digestive glands, is the result of a synthesis of the local nervous and central neurohumoral influences.

Glands of the large intestine. The composition and the course of secretion of the large intestine was studied mainly in Pavlov's laboratory (N. Strazhesko et al.) by the fistula method and was supplemented by observations of people in whom, as a result of a surgical operation (because of intestinal obstruction), an artificial anus (*anus praeternaturalis*) was made in the lower segment of the small or large intestine.

The juice of the large intestine, like that of the small intestine, consists of solid and liquid parts. Since the number of mucous cells prevails in the large intestine, its juice contains considerably more mucous clumps than the juice of the small intestine. The liquid part of the juice is semitransparent, strongly opalescent and alkaline. The solid part, in addition to mucus, contains a large amount of bacteria, disintegrated cells (detritus), white blood corpuscles and remains of the undigested food.

The juice of the large intestine contains weak proteolytic enzymes—erepsin and nuclease. The lipolytic action of the juice is very weak; of the amylolytic enzymes amylase, maltase and invertase have been found. There is no enterokinase. The amount of juice secreted is small: 0.05 to 0.15 ml. of juice is secreted in the dog per hour. The secretion of the juice is conditioned mainly by mechanical stimuli.

Movements of the Intestines

The foodstuffs which have entered the intestines remain there for a considerable time. In herbivores the chyme may be retained in the intestines for several days; in man, after eating certain foodstuffs, the remains of the digested food may stay in the intestines for more than 24 hours.

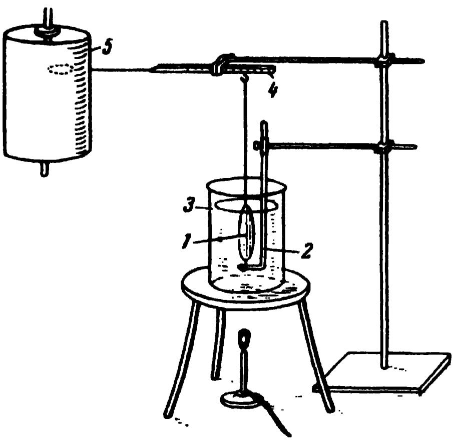

Fig. 126. Diagram of methods used in recording movements of isolated intestine

1—portion of intestine fastened to stanchion *(2)* in glass *(3)* filled with warm Ringer's o Thyrode's solution; intestinal movements are transmitted to lever *(4)* whose oscillations are recorded on kymograph *(5)*.

The motor function of the intestines is effected by the smooth muscles arranged in two layers. The outer muscle layer consists of fibres arranged longitudinally, the inner layer is composed of muscles whose fibres encircle the lumen of the intestines.

Various methods are used in the study of the intestinal movements: 1) observation of the intestinal movements in animals with an open abdominal cavity immersed in a warm salt bath; 2) observation of the intestinal loop brought out surgically under the skin; 3) observation through a celluloid window grafted into the abdominal wall; 4) recording the movements of the excised intestinal loop placed in a vessel with Ringer's solution or the solution of Thyrode (Fig. 126); 5) registration of the changes of pressure in a balloon inserted in the intestine; 6) observation or photography with the aid of X-rays after a preliminary intake of food mixed with radiopaque substances, for example, $BaSO_4$ (roentgenography and roentgenoscopy). The last method is widely used for diagnostic purposes in man.

Movements of the small intestine. The following movements of the intestine are distinguished:

a) *pendular movements,* expressed in rhythmic lengthening and shortening, simultaneously embracing a considerable portion of the intestine;

b) *fluctuations in the tone*, as seen in protracted changes in the length and the lumen of separate intestinal segments. The tone of the intestine conditions at each given moment a definite volume of the intestines. The tonic state, peculiar to the intestinal musculature, like the musculature of the other abdominal organs (stomach, gallbladder, etc.), is characterized by so-called plasticity. This property conditions for a long time not only the distention of the walls, but also of the lumen (the volume) of the intestine conformably to the food filling it;

c) *peristaltic movements* (Fig. 127) occur in the longitudinal and the transverse musculature of the intestine. In these movements the rhythmic contractions of the circular muscles lead to a diminution of the intestinal lumen at a definite restricted point while the adjacent section relaxes and distends at the same time, owing to which the contents of the constricted part are pressed out into the distended part. Then comes the contraction of the segment which was in a state of relaxation, while the subjacent segment relaxes. This alternation of relaxation and contraction follows regularly from the duodenum to the large intestine. The contractions followed by relaxations spread from the point of their origin along the entire intestine or at least over a considerable distance (peristaltic waves). These movements resemble the movements of a rain worm. Once begun, the peristaltic waves follow each other at a definite rhythm and rate.

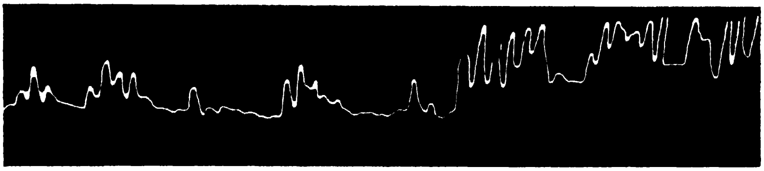

Fig. 127. Record of movements of the small intestine in the dog.

If we observe with the aid of X-rays the intestine of the cat or the dog, who were given bread and milk with a mixture of barium sulphate, we shall note that at a certain moment the continuous column of the food mass is broken up by the movements of the intestine, forming a chain at this segment of the intestine. Within the following few seconds each of the links breaks in halves and the halves of the two neighbouring segments form a new link (Fig. 128).

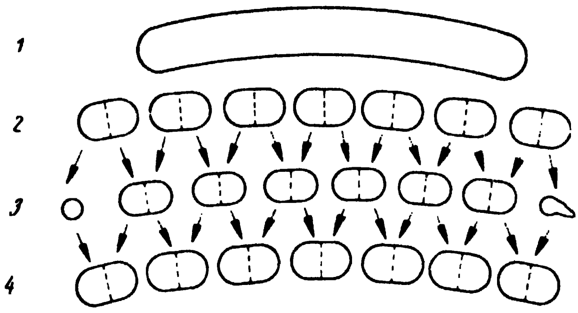

Fig. 128. Diagram depicting process of rhythmic segmentation.

Rows *1*, *2*, *3* and *4* show sequence of rhythmic segmentation phenomena in intestine. Dotted lines show boundaries of division. Arrows indicate serial derivation of segments (after W. Cannon).

This *segmentation* (Cannon) effected by tonic contractions may spread along the entire intestine. Due to this process there is close contact of the food mass with the wall of the intestine and its contents; this is also aided by the pendular movements which mix the chyme.

These movements do not, however, cause the chyme to move along the intestine, because the chyme column which is rather long or broken up into parts can remain in the same intestinal segment for a long time. The food mass advances only because of the peristaltic waves which spread along the entire intestine or over a considerable portion of it.

The peristaltic movements are stimulated mainly by the mechanical stimulation of the intestinal wall. If the chyme is very poor in solids (in other words, if nearly all the solid foodstuffs have been dissolved) the peristalsis of the intestine sharply decreases. The significance of bulkage substances (mainly cellulose) is that their presence in the chyme considerably increases peristalsis.

Alvarez has shown that the excitability of the intestine directed from the stomach to the rectum changes. Excitation arising particularly easily in the upper part of the intestine acts as a trigger, as it were, and then the tonic tension upon reaching a certain value changes into a peristaltic wave.

The peristaltic wave usually spreads from the oral end to the anal. Normally there is no antiperistalsis in the small intestine. If a small portion of the animal's intestine is excised and then sutured in the same place but in the reverse direction so that the anal end is closer to the stomach a local hindrance arises in the peristalsis, since the peristaltic wave, which began higher than the point of operation, cannot spread along the portion of intestine sutured in the reverse direction. If such an animal swallows a bone with its food it may perish from ileus.

Peristalsis may proceed for a short time in the opposite direction, from the anus to the stomach; this is so-called antiperistalsis, which is observed, for example, in vomiting (p. 272).

Mechanism of motor activity of small intestine. The excised portion of the intestine, suspended in Ringer's solution through which oxygen is passed, shows regular rhythmic movements. Like the work of the heart the motor activity of the intestine cannot normally be considered autonomous because in the organism it depends on the rest of the digestive apparatus and the body as a whole.

What elements stimulate intestinal movements?

If the muscular layer is so dissected as to eliminate from it the nervous plexus the rhythmic movements (but, apparently, not the peristaltic) can still occur for some time and the smooth muscles, deprived of the nerve elements, continue to respond to the application of such substances as pilocarpine, choline, etc. It could, therefore, be assumed that the muscle elements themselves are possessed of automatism. However, it is impossible to speak of a neurogenic or myogenic origin of impulses in the rhythmic activity of the smooth muscles of the intestine, opposing them to one another as mutually exclusive, since its complex neuromuscular apparatus works as a single whole.

Mechanical stimulation is the primary factor which causes the movements of the intestinal musculature. Pressing on the intestine or even touching it causes contraction at the given point and relaxation in the subjacent point. Introduction of a bolus of sufficient size into the upper opening of an isolated portion causes its ejection through the lower opening. Chemical stimulation is another factor: entrance of acids of weak concentration, alkalis and a number of other substances into the intestine causes an increase in the peristaltic movements.

Choline and acetylcholine, the substances formed in the wall of the intestine itself, and adrenalin, produced in the adrenal glands, are particularly strong chemical stimuli for the muscular apparatus of the intestine.

Acetylcholine or carbocholine increase the movements of the intestine in a solution of $1:10^5$. Adrenalin, on the contrary, depresses peristaltic movements and lowers the tone in a solution of 1:10^6. Acetylcholine and adrenalin, as the transmitters of stimulation, in the given case substitute, as it were, for the stimulation of the vagi and the sympathetic nerves.

The movements of the intestine are produced by contraction of the longitudinal and circular muscles located under the serous membrane. The less powerful layer of muscles—*muscularis mucosae*—is of importance in special stimulations; for example, a pin introduced into the intestine of an animal may pass through the entire intestinal canal without injuring its wall: stimulation of the intestine by the point of the pin causes these muscles to contract; as a result the pin is placed parallel to the length of the intestine and is pushed towards the anal opening.

The complex movements of the intestine, its peristaltic waves regularly running from the stomach to the anal opening are conditioned by a peculiar complex nervous apparatus contained in the walls of the intestine (intramural innervation) and by influences of the central nervous system (extramural innervation).

Regulation of Intestinal Movements

The movements of the small intestine are dependent on the central nervous system. Reflex influence regulates the intestinal movements under the action of the internal and external environment on the organism.

Stimulation of the vagus increases the peristaltic waves and raises the tone of the intestine (Fig. 129) while stimulation of the splanchnic nerve, on the contrary, depresses peristalsis and lowers the tone (Fig. 129). This correlation is dependent on the tone of the intestinal musculature.

The fibres of the vagi and the splanchnic nerve are in a state of lesser or greater tonic excitation. Cutting the vagi, therefore, slows down the movements of the intestines, whereas cutting the splanchnic nerve accelerates them: the influences accelerating the movements of the intestines are absent in the former case, while those inhibiting these movements do not act in

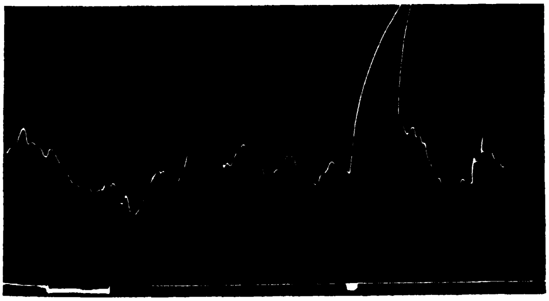

Fig. 129. Influence of splanchnic nerve (first, long record) and vagus (second, short record) on stimulation of movements of the small intestine in the dog.

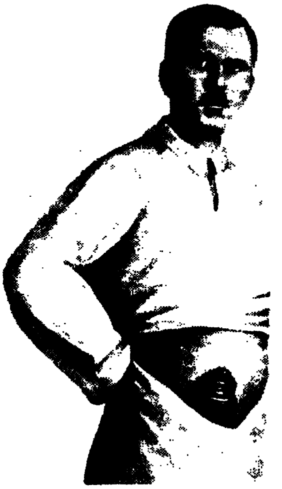

Fig. 130. Patient with exteriorized loop of intestine in region of the ileocaecal valve (after K. Bykov).

the latter case. The intensity of the nervous action on the intestines changes reflexly so that stimulation of the afferent fibres (for example, stimulation of the sciatic nerve) causes changes in the movements of the intestines. Strong stimulation of the afferent fibres usually inhibits these movements. The higher regulating apparatus, the cerebral cortex, also influences the movements of the intestines. It is possible to develop a conditioned reflex to the movement of the small intestine brought out under the skin in its portion which merges into the large intestine (Fig. 130). The influence of the cerebral cortex on the other portions of the small intestine is even greater.

The centres of the vagi and the sympathetic nerve may become excited when adrenalin, acetylcholine and other substances enter the blood. Accumulation of CO_2 in the blood at first causes increased peristalsis and evacuation of the contents from the small intestine into the large. That is why in death from asphyxiation the small intestine is found to be empty, since the content is voided into the large intestine during asphyxiation. In various psychic phenomena impulses run from the cerebral cortex accelerating or slowing down the movements of the intestines and at the same time involving humoral agents. When, for example, sufficient quantities of adrenalin enter the blood under reflex influence the intestines are sharply inhibited owing to the action of adrenalin on the structures innervated by the nervous apparatus of the intestine connected with the splanchnic nerve.

Movements of the Large Intestine

The contents of the small intestine pass into the large intestine through the ileocaecal sphincter. It was formerly supposed that the ileocaecal sphincter admitted the contents of the small intestine into the large purely mechanically because of its anatomic structure and prevented the passage of the intestinal contents in the opposite direction. It is well known, however, that the contents of the small intestine pass into the large only when the foodstuffs in the small intestine have been adequately digested.

Observations conducted in chronic experiments on dogs and on man with fistulas of the large intestine give reasons to believe that the mucous membrane in the ileocaecal region is not merely a mechanical valve, but a complex device which subtly regulates the passage of the contents from the ileum into the large intestine. In a patient with a portion of the intestine consisting of a small segment of the ileum, the caecum and the ascending colon brought out to the skin (in the course of surgical treatment) mechanical and chemical stimulation of the ileum caused the ileocaecal sphincter to close. It should be noted at the same time that the intestine reacts differently on both sides of the ileocolic sphincter (observations by Bykov and Davydov). When the ileum is stimulated at the point where it opens into the caecum the animal or man react strongly by feeling pain, whereas stimulation behind the ileocolic sphincter in the beginning of the large intestine causes no discomfort at all. Stimulation of the mucosa of the intestine near the ileocolic sphincter on the side of the ileum not only causes the contraction and closing of the ileocaecal sphincter, but also reflexly influences the pyloric sphincter. Mechanical or chemical stimulation in the region of the ileocolic sphincter on the side of the large intestine causes strong movements of this intestine, whereas peristalsis of the small intestine almost completely ceases at this time. Upon removal of the stimulus from the large intestine the movements of the small intestine begin.

Though we have only scant information on the activity of the ileocaecal sphincter, it is well known that stimulation of the splanchnic nerve, by causing the musculature of the intestines to relax, contrariwise conditions a strong contraction of the muscle fibres connected with the ileocaecal sphincter. The relation of the vagi to the ileocaecal sphincter has been studied but little as yet.

The contents of the small intestine pass into the large intestine gradually. When the ileocaecal sphincter relaxes separate portions of the contents of the small intestine are transferred into the large intestine by peristaltic contractions.

The movements of the large intestine are of the same nature as those of the small intestine. With the aid of X-rays we can trace in the cat, in the dog, and also in man, the way the chyme, after liberation from the ileum, first of all fills the nearest portion of the colon. Distension of this section causes a contraction of the ascending colon where it merges into the transverse colon. From here the waves slowly descend to the caecum producing, as it were, reverse peristalsis; the reverse waves transfer the chyme from the ascending and transverse colons to the caecum. These movements occur slowly and the chyme comes into close contact with the mucosa; owing to the absorption of water the liquid mass condenses.

Because of peristalsis the entire chyme moves into the ascending and further into the transverse colons. This peristaltic wave, however, is unable to drive the entire mass of the chyme to the end of the large intestine and by antiperistaltic waves the chyme is moved for some distance back again. A sufficient amount of a denser mass (as a result of water absorption) accumulates here again and then a peristaltic wave drives the dense mass still farther in the direction of the rectum.

As a result a large part of the contents is accumulated at the distal end of the large intestine near the sigmoid flexure. The dehydrated part of the contents is separated by segmentation from the portion of the intestine which contains the chyme. About 4,000 gr. of chyme move past the ileocaecal sphincter in man in 24 hours.

A portion of the large intestine excised from the body continues to move. Hence, the same phenomena are discovered in the large intestine deprived of innervational connections as in the small intestine. The longitudinal folds (*striae longitudinales*), composed principally of elastic muscle fibres, aid in shortening the intestine. But when contraction of the circular layer compresses the intestine the longitudinal folds, located lower, aid in dilating its lumen.

The extramural innervation of the large intestine is effected by the sympathetic and parasympathetic fibres of the hypogastric and the pelvic nerves which arise from the lumbar and the sacral portions of the spinal cord, and also by fibres of the vagi. Depending on the tonic tension of the intestinal muscles the above-mentioned conductors either increase or decrease the movements of the large intestine. The inhibiting influences are transmitted, chiefly, along the hypogastric nerve; the stimulating influences are communicated through the vagus to the upper segments and along the pelvic nerve to the lower segments. The centre of the spinal cord, where the impulses to the ileocaecal sphincter are relayed, is in the segments of the spinal cord from the XII thoracic or from the I to the III and IV lumbar vertebrae.

Impulses, which exert a strong influence on the activity of the gastric glands, run from the interoceptors of the small and the large intestines, as well as from the rectum. Depending on the force and frequency of the impulses, as well as on the state of excitability of the gastric glands, the influence of these impulses may be weak or sufficiently strong. The complex interrelation of the separate parts of the digestive apparatus, regulated by the central nervous system, characterizes it as a single whole.

Production and Composition of Faeces

The chyme in the large intestine gradually changes into a faecal mass. When the contents, liberated from the small intestine into the large, are dehydrated, only 150 to 200 gr. of faeces remain of the 4,000 gr. of the chyme.

The faecal mass usually consists of: a) the remains of the undigested food (fibres of cellular tissue, separate muscle and tendon fibres, grains covered with cellular tissue and containing starch, protein, fat, chlorophyll and insoluble lactic salts) and b) the products of the intestinal activity itself (mucus, desquamated cells of the mucous membrane of the intestines, cholesterol, coprosterol, urobilinogen, cholic acids, enzymes, as well as live and dead bacteria, the latter constituting a considerable part of the faeces—close to 30 to 50 per cent). The consistency and composition of the faeces may vary with the composition of the food.

Vegetable food causes the formation of a greater quantity of faeces than does animal food. Milk yields a relatively large amount of faeces because of the large quantity of unabsorbable salts it contains. Animal proteins are utilized up to 98 or 99 per cent, while vegetable proteins are assimilated to a lesser extent. The extent of assimilation may widely vary in the same person if the same foodstuffs are consumed for a long time. The unassimilable substances are strong stimuli of the intestinal musculature, and the mass of the food consumed and reaching the large intestine is, therefore, very important.

Role of Intestinal Microflora

The distribution of the normal microflora along the digestive tract may be represented in the following scheme: 1) abundant and extraordinarily diverse microflora in the oral cavity; 2) scant microflora in the stomach, 3) small number of bacterial species in the small intestine, and 4) extraordinarily rich and diverse flora in the large intestine.

Most of the microbes that enter the stomach are killed by the HCl. Sarcinae, cocci, yeasts, representatives of the group of bacteria—*B. mesentericus subtilis*, etc., have been found in the stomach. A very scant flora consisting of few bacilli and cocci, which produce lactic acid, are found in the upper segments of the small intestine.

In injuries to the pyloric portion of the stomach or in disorders of the small intestine the microbes move from the lower segments of the intestine to the upper and to the stomach. The pyloric antrum, as well as the ileocolic sphincter, may be regarded as the natural barriers to the penetration of microbes into the divisions of the intestines where they are not normally present.

The microflora in the large intestine and in the faecal mass is quite abundant; there is an average of 15,000 million microbes per 1 gr. of faeces. The flora of the large intestine includes the important *B. coli*, a microbe related to microorganisms pathogenic to man. The bacteria capable of causing the putrefaction of proteins, are most frequently encountered in the large intestine. There are also many other bacteria.

The bacteria play some part in splitting the nutritive substances. They split the hydrocarbons which are inaccessible to the fermentative hydrolysis by the digestive juices; besides, the hydrolysis with the aid of the microbes does not stop at the monosaccharide stage but continues until lactic, oleic, succinic and other fatty acids, hydrogen, methane, carbon dioxide and other gases are formed. The polypeptides and amino acids disintegrate during protein putrefaction and substances with the characteristic faecal odour are formed. The action of the bacteria in the intestine results in the production of scatol and indole from tryptophane, phenol and paracresol from tyrosine, hydrogen sulphide and other gases from the amino acids which contain sulphur. A number of bases known as proteinogenic amines, for example, cadaverine, are sometimes formed from the amino acids, especially from lysine and histidine. A considerable part of the phenol-type substances, which are not immaterial to the organism, is absorbed and rendered harmless in the liver with the formation of less harmful ether-sulphuric acids.

The microflora of the intestine may vary partly with the food consumed, one type of bacteria supplanting another. Thus, for example, the microbes which cause lactic fermentation supplant the bacteria which cause putrefaction.

The question of the role of microbes as normal inhabitants of animal organisms arose as far back as the time of Pasteur. Experiments with raising animals under sterile conditions, for example, guinea-pigs extracted from the wombs of their mothers under aseptic conditions, have yielded contradictory results. It turned out that in most cases the animals kept under sterile conditions developed worse than did the control animals that lived in their natural environment. In evaluating the results of these experiments we must bear in mind, however, that their authors did not take into consideration the vitamin requirements of the animals.

The bacterial flora and the simplest microorganisms (Infusoria, etc.) are of great importance to the processes of digestion in herbivores. Whereas cellulose is but weakly split up under the action of bacteria in man, in the stomach and intestines of herbivores this process is of enormous importance. The conversion of cellulose, which forms the walls of many vegetable cells, liberates the protein, fats and carbohydrates. The herbivores have very long intestines. Thus, for example, the intestines of the omnivorous pig is 14 times as long as its body, those of the goat and sheep are 27 times as long, and those of the rabbit 31 times as long. The food stays in this enormous cavity for several days and is subjected to fermentation, which enables the herbivorous animals to utilize foods that cannot be utilized in the intestines of man and carnivores.

An increase in the number of bacteria may interfere with the assimilation of nutriments; besides, the bacteria produce toxins. The putrefaction of protein bodies and the appearance of toxic products may cause auto-intoxication, which, as I. Mechnikov believed, may be one of the reasons for the ageing of cells. Various authors also point out the harmful effects of a meat diet and recommend the substitution of one microflora for another by consuming dairy foods (sour milk, etc.). The intestinal microflora, no doubt, plays an important part in the organism by ensuring nourishment for the herbivores, and indirectly for man, in connection with which this important physiological problem requires further study.

Act of Defaecation

The faecal mass collects, as has already been said, in the distal end of the large intestine before reaching the rectum. The movements of the distal end of the large intestine and the ejection of the faeces begin intensively only when the pressure of the faecal mass on the walls of the lower segment of the large intestine becomes strong enough by virtue of an accumulation of certain quantities of excrement. The contraction of the lower segment of the large intestine is, apparently, conditioned entirely by nervous influences resulting from the stimulation of the receptors of the large intestine. This stimulation causes a reflex shortening of the distal division of the large intestine due to the contractions of the recto-coccygeal muscle which are followed by contractions of the circular muscles from the upper end of the sigmoid flexure. Owing to this the contents of the large intestine are pressed out into the rectum; in man the urge for defaecation is caused by the entrance of a portion of the faecal mass into the rectum. This urge, probably, corresponds to the contraction of the rectal musculature. If defaecation, i.e., evacuation of the rectum, does not take place the muscles of the rectum relax and the faecal mass, which has entered it, remains. The entrance of the following portions of faeces from the sigmoid colon into the rectum will again cause the urge for defaecation.

In the act of defaecation the muscles of the rectum and perineum contract, the contraction of the anal levator muscle leading to a shortening of the rectum. At the same time the internal and external anal sphincters relax. Contraction of the abdominal muscles aids in pressing the faeces from the large intestine into the rectum and from the latter outside. Defaecation is, thus, executed by the simultaneous contraction of a number of smooth and striated muscles.

This complex act is coordinated by the central nervous system, the centres located in the lumbar and sacral portions of the spinal cord. The hypogastric and pelvic nerves arise from here; of these the former reach the sympathetic ganglia (inferior mesenteric ganglion), the latter—the ganglia located in the walls of the intestine. Postganglionic fibres run from the cells of the ganglion.

For some reason or other the act of defaecation may become impaired. Thus, if the lumbar segment of the spinal cord is destroyed in animals or the region of the III to IV lumbar segments is diseased in man, they are unable to retain the faeces, cannot deliberately evacuate the rectum and defaecate irregularly and in small portions. If the lower portion of the spinal cord is affected, where the afferent fibres of the receptors of the rectum enter, the urge for defaecation is lost and as a result the evacuation of the intestines is impeded and constipation ensues.

Artificial stimulation of the nerves of the rectum may cause reflexly both the contraction and relaxation of the muscles, depending on the condition of the nervous centres and the working organs.

The intramural nervous system and muscles of the large intestine and rectum play an especially important part when the functions of the centres in the spinal cord are impaired. If the spinal cord is destroyed the local nervous ganglia exert considerable influence on the muscle tone of the intestine and the sphincters owing to which normal defaecation may be largely restored.

The cortical influence on the act of defaecation is well known. The deliberate delay of the act of defaecation despite the desire to defaecate indicates that the cerebral cortex is involved in the functions of the sphincters and muscles of the intestine. Diarrhea caused by fright, retardation and involuntary defaecation in mental diseases also prove the cerebrum is involved in this complex coordinated act. Artificial development of conditioned reflexes for the act of defaecation confirms the observations as regards the influence of the cerebral cortex on this process.

Periodic Activity of the Digestive Apparatus on an Empty Stomach

The secretory and motor apparatus of the digestive system function not only during the process of digestion, but also on an empty stomach, outside the digestive process.

In Pavlov's laboratory in 1904, Boldyrev observed contractions of the stomach and intestines, secretion of mucus in the stomach (Fig. 131), as well as pancreatic juice and bile, in dogs with empty stomachs (outside the digestive period) every 1.5 to 2.5 hours for a period of 10 to 30 minutes. This periodic activity of the digestive tract was also studied in man (Boldyrev and Anichkov, Cannon, Carlson).

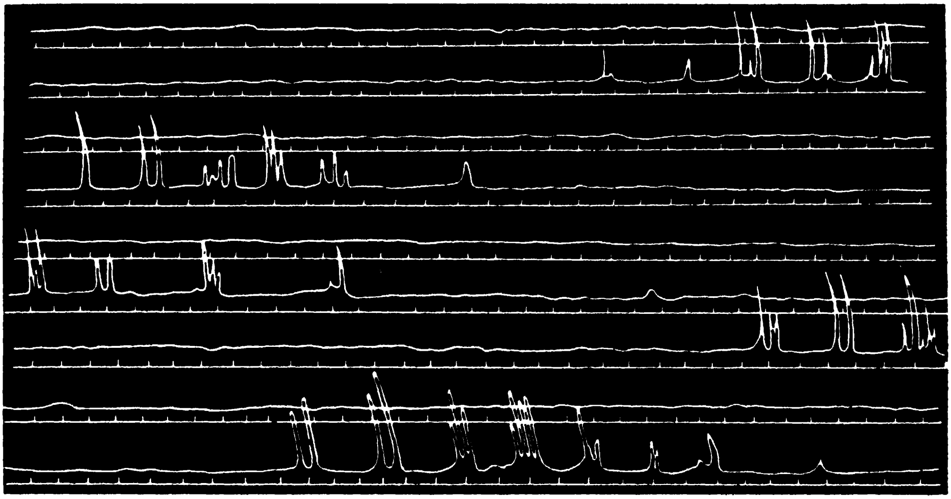

Fig. 131. Record of periodic ("hunger") movements in the dog outside the digestive period (after V. Boldyrev).

Cannon and others assume that the periodic contractions of the stomach, coinciding with the sensation of hunger, stimulate this sensation.

It should be noted that the factors which depress the periodic activity of the stomach at the same time either weaken or fully suppress the feeling of hunger. Excessive fatigue or continued starvation (for several days) suppress the feeling of hunger; under these circumstances there is no periodic activity of the digestive apparatus either.

The mechanism of periodic activity has not been explained as yet. Babkin believes that the periodic activity is primarily manifested in the movement of the stomach and the intestines, whereas the secretion of the digestive juices is the result of the ready secretion being pressed out of the ducts and folds of the mucosa.

The periodic contractions are, undoubtedly, influenced by the humoral stimuli which appear in the blood when the animal is hungry. Chukichev transfused the blood of a hungry animal to another animal and thus produced periodic movements in the latter. Contrariwise, the transfusion of the blood of a sated animal depresses or fully terminates the "hunger" movements.

The appearance of the phase of periodic activity depends on the action of conditioned stimuli. Thus, the processes, occurring in the cerebral cortex, may change the alternation of the periods of activity and rest, as well as the intensity of the motor reactions of the stomach and the duodenum (Bulygin).

The periodic activity of the digestive apparatus on an empty stomach is one of the vivid examples of periodically occurring processes in many executive organs, if not in all of them. It should be borne in mind that the periodic alternation of rest and activity of the digestive glands, as well as of the other executive organs, is controlled by the regulating nervous apparatus, especially by the higher division of the central nervous system—the cerebral cortex. The phenomenon of periodic activity must always be taken into consideration in laboratory investigations, as well as in prescribing diets, because by its physiological nature this phenomenon reflects a pattern differently developed and dynamically conditioned in each individual case.

The leading influence of the nervous system does not exclude the role of the humoral factors in the periodic activity.

The problem of this interesting phenomenon—periodic activity—is far from solved.

PART VI

ABSORPTION

CHAPTER 30

ABSORPTION

In the broad sense of the word absorption is the passage of various substances through a layer of cells into the blood. It is the passage into the blood of substances from the integuments of the body, from the various divisions of the alimentary tract, the internal organs (bladder, uterus, bronchi, lungs), the subcutaneous cellular tissue or muscles. *Absorption* of substances from the *intestines* is of the greatest physiological importance since it ensures the nutrition of multicellular organisms and serves to introduce medicines into the human body because of the most widespread oral method of administering medicine.

The rate of absorption depends on the histological structure of the given portion of the alimentary canal, the length of time the substances are retained in it and on the composition of these substances at any given moment.

There is hardly any absorption in the oral cavity and in the oesophagus. There is also very little absorption of food substances in the stomach, though some of them (alcohol, carbon dioxide and, to a lesser extent, water and chlorides) are very well absorbed by the gastric mucosa.

The small intestine is the chief organ of absorption. From five to eight hours after eating most of the chyme passing from the small into the large intestine hardly contains any absorbable substances with the exception of water which is vigorously absorbed in the large intestine.

Different portions of the small intestine vary in their ability to absorb different substances. For example, in the upper portion of the small intestine, all other conditions being equal, sugar is absorbed faster than water; in the lower portion water is, on the contrary, absorbed faster than sugar. Sodium chloride is absorbed in the lower portion even faster than water.

The inner surface of the human intestines measures approximately 0.65 m^2. But since Kerkring's folds project into the cavity of the intestines and the entire surface of their mucosa is covered with a tremendous number of villi (18 to 40 per 1 mm^2) the total surface of the intestines is much larger and reaches 4 to 5 m^2.

The villi cover most of the surface of the intestinal mucosa. The length and diameter of a villus (in man) measures 0.2 to 1 mm. The entire surface of the villi is covered with cylindrical epithelium. The epithelial cells contain fibrils (Fig. 133), a so-called mitochondrial apparatus which changes during absorption.

Each villus has a lymphatic vessel and an artery. The lymphatic vessel begins in the villus by a single large swelling. Under the villus this vessel forms a large plexus and further down—another, a submucous plexus. In the submucous plexus the lymphatic vessels have valves owing to which the lymph flows only in one direction. Before entering the thoracic duct (*ductus thoracicus*) the lymphatic vessels necessarily pass through a lymph node.

The artery, which enters a villus, reaches its summit and ramifies, partly passing into the capillary network and partly forming a direct arteriovenous anastomosis with the main vein which also begins at the summit of the villus.

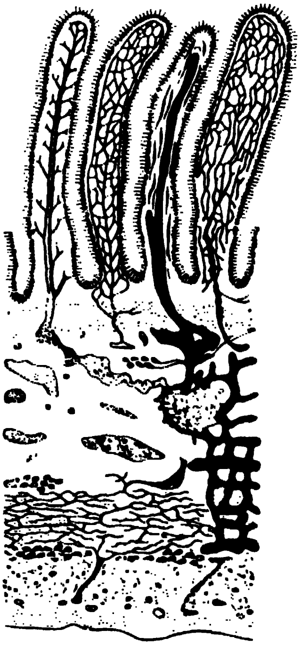

Fig. 132. Structure of a villus (after Verzar).

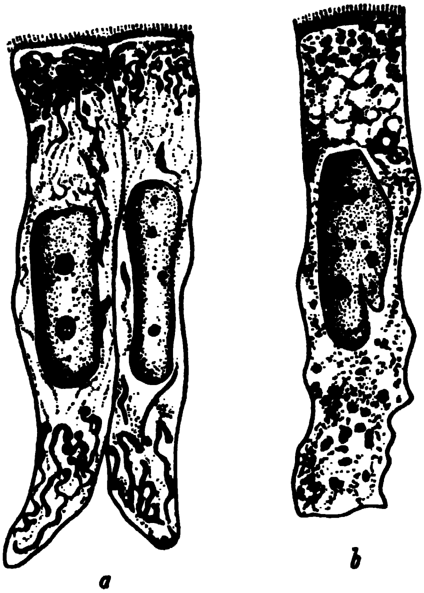

Fig. 133. Fibrillar structure of an intestinal epithelial cell during absorption (*a*) and on an empty stomach (*b*).

Inside the villi there are some small smooth muscle fibres and a network of nerves connected with Meissner's plexus. Meissner's plexus forms nervous paths in between the mucous and submucous layers of the intestines and sends to the villi fibres located under the epithelium around the central lymphatic vessel.

Mechanism of Absorption

Physiologists sought for the answer to the question of the mechanism of absorption primarily by studying analogous mechanisms of filtration of various substances through organic or inorganic membranes, i.e., the phenomena of filtration and osmosis.

Mechanism of filtration. The mechanism of filtration consists in the passage of a solution through pores under the action of some mechanical pressure. The rate of filtration depends on the amount of this pressure and the size of the pores. If the dissolved particles are larger than the pores they do not filter. If filtration occurs it results in similar concentrations of the solute and the solvent on both sides of the membrane.

In the intestines there are forces capable of exerting a certain mechanical (hydrostatic) pressure. These include the action of the abdominal wall, intestinal peristalsis and the suction movements of the villi. As a result of peristalsis the intra-intestinal pressure usually reaches 4 to 6 mm. Hg but the blood pressure in the capillaries of the villi is higher (8 to 15 mm. Hg). Basing himself on this difference Starling concluded that the hydrostatic forces could not ensure absorption. We must take into account, however, that the pressure in the lymphatic space of the villi is much lower than it is in the capillaries.

It goes without saying that absorption is accelerated when the hydrostatic pressure is raised experimentally. A 0.9 per cent solution of sodium chloride is absorbed twice as fast when the pressure in the intestines is raised from 3 to 8 mm. Hg. However, there is no constant hydrostatic pressure in the small intestine and the mechanism of filtration is rather a supplementary factor.

The movements of the villi play an essential part (Verzar). By contracting and expanding the villi now press blood and lymph out of themselves, now suck in the substances dissolved in the intestines (this phenomenon resembles filtration of solutions into a retort connected with a water-jet pump).

The movements of the villi vary. In dogs they continue for 2 to 4 hours after feeding, though not all the villi move simultaneously, but in groups—each group independently of the others. A strong stimulus sets all the villi in motion. Normally they move 3 to 5 times per minute. Exsanguination of the mucosa leads to a rapid cessation of the suction movements of the villi.

Chemical stimuli found in the intestinal cavity and acting on the villi with the aid of the nervous structures of the intestines are the natural stimuli of the movements of the villi. The chemical stimuli of the movements of the villi include yeast extracts, peptone solutions, histamine, bile acids, a number of amino acids, as well as several pharmacological substances, for example calomel. The movements of the villi are inhibited by the salts of calcium and potassium.

The villi move under the influence of nerve impulses which may arise not only in the central nervous system, but also in Meissner's plexus. Touching the top of a villus with a hair produces no effect, whereas touching its base causes the villus to contract, and the stronger the stimulus, the more villi react. If droplets of an yeast extract or crystals of histamine are applied to the top of a villus it is precisely this villus that begins to move and the movement intensifies as the substance dissolved in the liquid, which surrounds the villus, comes closer to its base. This phenomenon is connected with the function of Meissner's plexus.

When a piece of the mucosa between the mucosa and the submucosa is denervated the villi immediately cease to move, while in the adjacent innervated sections the villi continue contracting.

There are reasons to believe there is also a humoral mechanism in the regulation of the movements of the villi. It has been found that under cross circulation the blood of a fed dog causes the villi to move when it comes to the isolated portion of a hungry dog's small intestine. Contrariwise, the blood of a hungry dog stops the movements of the villi when it comes to the intestine of a fed dog. Introduction of hydrochloric acid into the duodenum intensifies the movements of the villi. A duodenal extract injected intravenously also provokes their strong movements. This gave rise to the idea that the mucous membrane of the intestines produced a hormone which influenced these movements. This hormone is neither like histamine nor like secretin. It has been named *villikinin.*

The movements of the villi are not the only mechanism of absorption since absorption occurs even when the villi are paralyzed. But their movements are very important in that they accelerate absorption. This is evident from the fact that an yeast extract, which intensifies the movements of the villi, considerably accelerates absorption. Thus, for example, in the presence of a 1 per cent yeast extract of all the peptone introduced into the stomachs of rats, 58 per cent was absorbed, while without the simultaneous introduction of the yeast extract only 31 per cent was absorbed.

According to Verzar's calculations, the dog's intestines 200 cm. long and 5 cm. wide contain (very roughly) about one million villi, while the volume of each villus' lymphatic space corresponds to approximately 0.005 mm.^{3} Consequently, the volume of the cavity of the villi is 5 ml. Since the content of the lymphatic space is pumped into the wall and thence into the lymph at each contraction of the villi, while the villi contract 3 to 5 times per minute, it follows that 15 to 25 ml. of liquid can be absorbed per minute.

The importance of *osmosis* and *diffusion* in the processes of absorption cannot as yet be accurately determined because in living beings osmotic pressure itself depends on many factors; biological membranes are membranes with variable permeability; they can dissolve a number of substances in themselves. In a way this decides the old controversy as to whether it is possible or impossible to explain the phenomenon of absorption by physicochemical mechanisms. Under conditions of a "living system" these physicochemical mechanisms become so complicated that they are not fully governed by any laws discovered in nonliving models, but acquire their own specificity not as yet subject to full analysis.

In some relatively simple cases, however, the significance of the phenomena of osmosis in the process of absorption comes sharply to the fore. The general osmotic pressure of the blood in the capillaries, especially if osmotic pressure of the colloids is taken into consideration, is much higher than the osmotic pressure of the chyme. The passage of water from the chyme into the blood is, therefore, quite simply explained by osmotic forces. The colloids of the blood, apparently, play an enormous role in the process of absorption since it has been experimentally shown (and substantiated by the physicochemical theory) that the proteins can ensure a redistribution of individual ions in the direction opposite to the difference in osmotic pressure. It has been, furthermore, established that a hypertonic solution introduced into the intestine becomes isotonic (Heidenhain). This fact is easily explained on the basis of the usual osmotic conceptions; it is much harder to explain the opposite phenomenon—the absorption of salts from a hypotonic solution.

Solubility of various substances in the cells of the intestinal epithelium is of considerable importance to the processes of absorption. Some investigators believe that the substances insoluble in cellular lipoids, which form the outer layer of cells, are absorbed only through the intercellular spaces, while the substances which do dissolve in lipoids (for example urea, glycerol, alcohol) are absorbed by the epithelial cells. The fact that only lipoid-soluble substances can be found in epithelial cells during absorption speaks in favour of this assumption.

The problem of change in permeability as a factor, which in its turn alters absorption in the intestines, was studied relatively little until recent years. But it is, undoubtedly, possible to choose conditions which change the processes of absorption because of the altered permeability of the intestinal wall. Such, for example, is a sharp acceleration in the absorption of sugar after injecting small doses of saponin.

The nervous system, no doubt, exerts a regulating influence on the complex process of absorption as a whole and, probably, alters the permeability of the intestinal cells. Saponin changes the permeability of epithelial cells which makes for intensified absorption of glucose and water. By using saponin as an unconditioned stimulus, but injecting some indifferent stimulus before saponin is introduced into the intestines, it has been possible to develop a conditioned reflex for an intensified absorption of glucose and water (Bykov). This proved the regulatory role of the cerebral cortex in a process so seemingly "independent" of it as the absorption of substances from the intestines into the blood. This reflex occurs according to the principal laws of conditioned-reflex activity: it can be suppressed, restored or differentiated.

It is also possible to develop a conditioned reflex for a delay in the absorption of glucose and water. In this case iodo-acetic acid may be used as an unconditioned stimulus, which delays the absorption of glucose when injected into the intestines or the blood. Any agent introduced many times simultaneously with iodo-acetic acid causes approximately the same retardation in the absorption of glucose as does the acid because of the development of a conditioned reflex. The impulses from the cerebral cortex, apparently, influence the permeability of the intestinal wall through a number of intermediate central and peripheral structures.

Absorption of Carbohydrates

Carbohydrates are absorbed through the wall of the intestines almost exclusively in the form of monosaccharides into which all carbohydrates are changed after being hydrolyzed by the diastatic enzymes of the intestinal and, mainly, the pancreatic juice.

Absorption of carbohydrates (monosaccharides) is perfect. The chyme in the region of the ileocaecal sphincter no longer contains any glucose, as it was observed, for example, in patients with unhealing fistulas of the ileum. Even in the lower portion of the small intestine glucose can be detected only after abundant consumption of carbohydrates. Moreover, the upper divisions of the intestines absorb carbohydrates more intensively than do the lower divisions. Thus, according to London, 1 cm.^{2} of the mucosa can absorb 19.2 gr. glucose in the duodenum, and only 3.26 gr. in the jejunal end of the small intestine.

As long as the concentration of glucose in the chyme is not above 5 per cent the rate of absorption is directly proportional to the concentration. With the subsequent increase in concentration absorption is slowed down. When the intestine contains 6 per cent sugar, water begins to enter from the intestinal blood vessels into the lumens of the intestines, the water coming directly from the blood or from the sharply increased secretion of intestinal juice. This is the basis for the laxative action of large quantities of sugar. With a sugar concentration of up to 2 per cent its absorption proceeds parallel to that of water.

The characteristic feature of sugar absorption is that glucose, normally contained in the blood, is absorbed very much faster than the other monosaccharides. If we take the rate of glucose absorption as 100 the corresponding figures for the other sugars except galactose will be much lower: for example, 44 for fructose and 30 for xylose.

Since the various mono- and disaccharides have approximately the same diffusion coefficient the different rates of their absorption could not be explained for a long time. Lately many investigators have been explaining the selectivity of glucose absorption as compared with other monosaccharides by the fact that already in the process of absorption glucose changes to glycogen in the very cells of the intestinal mucosa. This maintains a constant difference in the concentration of the glucose in the blood and in the chyme which ensures rapid glucose absorption.

Experiments with poisoning animals with iodo-acetic acid which blocks the process of phosphorylation necessary to carbohydrate metabolism, speak in favour of this theory. It turns out that this acid inhibits the absorption of glucose. At the same time it has been found that an extract from the intestinal mucosa phosphorylates galactose and glucose, partly fructose, but does not affect manose, pentose or xylose. The addition of iodo-acetic acid fully stops phosphorylation of glucose by the extract from the intestinal mucosa. It must, therefore, be taken for granted that the delay in the absorption of carbohydrates under the action of iodo-acetic acid depends on the cessation of phosphorylation processes. When these processes stop glucose and the other carbohydrates, usually phosphorylated in the intestinal wall, are absorbed as slowly as xylose and pentose which are not subject to this process.

Absorption of sugar is under constant control of hormones. Removal of the cortical layer of the adrenals sharply reduces the absorption of glucose. Absorption of sugar is also affected by the vitamin B complex which stimulates glucose absorption. In B-avitaminosis the absorption of glucose decreases.

Carbohydrates are absorbed almost exclusively into the blood, and an increased sugar content is always observed in the blood after consumption of carbohydrate food. Changes in the glucose content of the lymph have been studied both in man with fistulas of the lacteals (Munk and Rosenstein) and dogs with an artificial fistula of the thoracic duct. It has not been possible to find any noticeable increase in the amount of carbohydrates in the lymph after abundant carbohydrate consumption, though there are indications that a small amount of sugar passes into the lymphatic vessels whence it rapidly enters the blood.

Absorption of Fats

Fats are absorbed almost exclusively in the small intestine with the fat passing mainly into the lymph rather than into the blood. This is easily observed if the animal is killed 3 to 4 hours after consumption of fatty food; the lymphatic ducts of the mesentery then look like white threads because they are filled with the emulsion of absorbed fat. This is why the lymphatic ducts of the mesentery are called lacteals.

Neutral fat as such is hardly absorbed at all. To be absorbed fat must be split up by the lipase of the pancreatic juice into glycerol and fatty acids. Glycerol is absorbed into the lymph, whereas the fatty acids in a free state are insoluble in the intestinal content. Nor are the soaps—the alkaline salts of the fatty acids—soluble in the intestinal chyme with its usual concentration of H-ions. Soaps dissolve in an acid medium only in the presence of bile and the latter must necessarily be present in the intestines for soaps and fatty acids and, consequently, fats to be absorbed. This is borne out by the following fact: if we tie up the bile duct and create an anastomosis between the gallbladder and the lower portion of the small intestine the fats will be absorbed (which can be judged by the filling of the lacteals with fat) only below the point where the bile is artificially drained (Dastre). However, bile alone without the action of the pancreatic juice is not enough to ensure the absorption of fat because the latter cannot be split up by lipase. Absorption of fat necessarily requires the action of both pancreatic juice and bile. Bile is necessary for the absorption of fat also because the lipase of the pancreatic juice is nearly inactive without it.

The action of bile on the absorption of fat is based on the fact that the bile acids change the fatty acids to soluble compounds which can penetrate through the intestinal wall.

Owing to the action of the various bile acids the fatty acids can be absorbed both in alkaline and acid media. The alkaline soaps of the fatty acids dissolve within the limits of $pH = 11.0$ to 8.0; a combination of desoxycholic, cholic and fatty acids dissolves only in alkaline and neutral media with a $pH = 7.1$ to 7.9 and does not dissolve in an acid medium with a $pH = 7.0$, but complex compounds of fatty and the twin bile acids dissolve in an acid medium with a $pH = 5.9$ to 6.1. Thus, fatty acids can be easily changed to soluble compounds at various levels of the pH medium in the intestines.

To change one mole of fatty acid to soluble form requires, according to Verzar's experiments, 3 moles of glycocholic acid (approximately 4 gr. per 1 gr. of fat). It has been computed on this basis that it would require 240 gr. of bile acids to dissolve 48 gr. of fatty acids (50 gr. fat). This corresponds to a secretion of about 12 litres of bile, while no more than 1.5 litres of bile is secreted in man per day. It has been shown, however, that one gr. of bile acids suffices to dissolve one gr. of fatty acids in the intestines, and not 4 gr. as *in vitro*. This is explained by the fact that not all the fatty acids are dissolved by the bile acids at the same time. After part of the fatty acids, dissolved in the bile acids, passes into the epithelial cells the complex compounds of fatty and bile acids break up. The fatty acids are synthesized into neutral fat in the intestinal cells, while the bile acids are liberated and, apparently, absorbed on the surface of the epithelial cells dissolving new molecules of fatty acids, etc.

At any rate, the fatty acids are liberated from the complex bile acid compounds in the intestinal mucosa and recombine with glycerol to form neutral fats. The addition of substances, which accelerate the synthesis of fats, increases the absorption of fatty acids. These substances include glycerophosphates. During intensive absorption of fat the total amount of fat and phospholipids in the lymph increases. In addition, lecithin is found in the intestinal mucosa itself. It is, therefore, quite probable that the phospholipids form a phase in the synthesis of neutral fat in the cell and that the synthesis of neutral fat, like that of carbohydrates, also goes through a stage of phosphorylation.

If this be so, iodo-acetic acid must inhibit the absorption of fats as we have described it with reference to glucose. Verzar's experiments have demonstrated that the lymphatic vessels of animals, who were subcutaneously injected iodo-acetic acid before being fed with fat, were deprived of fat. It has been established by histological analysis that these poisons do not delay the passage of fatty acids into cells, but inhibit the phosphorylation of neutral fat.

The question of the mechanism of fat absorption is still not clear in many respects. It is very possible that there are other important processes which ensure the passage of fats through the intestinal wall. Many authors have ascribed certain importance in this respect to leucocytes found in abundance in the intercellular spaces of the epithelial cells. It has been noted of late that the lecithin of the bile also sharply increases the absorption of fatty acids.

The important feature of the absorption of fats consists in the fact that, unlike proteins and carbohydrates, they are not absorbed directly into the blood, but into the lymphatic space of the villi and thence along the lacteals are emptied into the blood through the thoracic duct. Besides, most of the fat is contained in the chyle as such, rather than as a mixture of the products of its disintegration. This fact, like the histological observation, which discovers droplets of fat in the epithelial cells of the intestines, warrants the conclusion that in the intestinal wall the principal mass of the absorbed fat is resynthesized from glycerol and fatty acids. The passage of fat into the lymph is also proved by the presence of fat in the lymph collected from the thoracic lymph duct where the greater part of the intestinal lymph is emptied through lymphatic ducts. This increase in the content of fat in the lymph of the thoracic lymph duct was observed in a man who had a fistula of the duct and in dogs in whom the opening of the duct was sewn into the skin.

It is possible, however, that a certain amount of fat passes directly into the blood.

There are no definite data on the upper limits of fat absorption. We may assume that the healthy human intestines can absorb 100 to 150 gr. of fat per day with a 95 to 98 per cent coefficient of utilization. Insufficient liberation of bile into the intestines or the absence of pancreatic juice sharply derange the absorption of fats, which the foregoing makes clear. In this case large quantities of unabsorbed fat are found in the excrements.

Absorption of Proteins

Despite the fact that proteins are intensively digested in the stomach the products of their conversion are not absorbed from the stomach because the protein derivatives formed in the stomach by the action of pepsin are still too complex. For practical purposes we should therefore take into consideration only the processes of absorption that occur in the intestines.

The amino acids absorbed from the intestines pass directly into the blood, as was recently proved by an analysis of the blood from the portal vein. However, the increase in the nonprotein nitrogen of the blood is not very large (5 to 15 mg. per cent) since the amino acids entering the blood from the intestines are very rapidly bound by the cells of the body, mainly by the cells of the liver. Small amounts of amino acids constantly pass from the liver into the blood. London also assumed there was some synthesis of proteins in the intestinal walls.

Animal proteins are, as a rule, absorbed somewhat better than vegetable proteins (of the latter the poorly converted proteins of cellulose are not absorbed). The products of animal-protein conversion (meat, milk, eggs) can be absorbed more than 90 per cent.

Absorption of Water and Salts

The absorption of water begins in the stomach, but since it passes very rapidly into the intestines it is mainly absorbed in the latter.

Enormous quantities of water can be absorbed from the intestines (in man 15 to 20 litres per day). Processes of osmosis, apparently, form the principal mechanism of water absorption since the osmotic pressure of the blood is usually higher than that of the chyme. When a considerable quantity of poorly absorbed salts, for example, Na_2SO_4 or $MgSO_4$ is administered, the osmotic pressure in the intestines sharply rises and the water passes into them from the blood. This partly determines the laxative effect of these salts. We must not forget, however, that the water content in the intestines may increase not only because of diffusion from the blood through the intestinal wall, but also owing to an intensified secretion of intestinal juice.

Most of the substances absorbed from the intestines pass into the blood and lymph in the form of aqueous solutions. If the dissolved substance is absorbed rapidly, the solution becomes hypotonic and the water also rapidly leaves the intestine. If the dissolved substances are absorbed slowly the water is retained in the intestine by the salts and maintains an osmotic equilibrium between the blood and the intestinal content. For example, from an isotonic solution of xylose (4.5 per cent) the water is not absorbed for an hour though more than half the sugar disappears during this time. Large amounts of water rapidly enter the intestinal lumen and the volume of the intestinal content increases. This shows that water cannot be absorbed even from isotonic solutions if the dissolved substances (in this case xylose) pass into the blood slower than the salts pass from the blood into the intestine. Consequently, water is absorbed the fastest from the hypotonic solutions of substances which rapidly diffuse through the intestinal wall.

The salts of alkaline metals are absorbed into the blood through the cells of the intestinal epithelium and not through the intercellular spaces. The higher the rate of diffusion the faster is the given ion absorbed. The salts of haloid acids are absorbed better than sulphates or carbonates.

Under certain conditions salts, especially sodium chloride, can pass from the blood into the intestine, sometimes in very large quantities, thus equalizing the osmotic pressure between the blood and the intestinal content. The intensity of absorption of a sodium chloride solution rises with the increase in concentration up to 1 per cent. Absorption ceases if the concentration of the sodium chloride solution increases to 1.5 per cent. In this and in higher concentrations the sodium chloride solution acts as a stimulus to intestinal juice secretion.

The salts of calcium are absorbed only in relatively small quantities so that this is not attended by any sharp increase in the content of calcium in the blood. It has been demonstrated in recent years that the salts of calcium are absorbed best when considerable amounts of fat are consumed with food; a soluble salt of calcium and fatty acid is, apparently, formed in this case. The facts obtained in experiments using isotopes have shown that iron is absorbed in considerable amounts only if the organism needs it.

Absorption in the Large Intestine

It may be assumed at the present time that there are, apparently, no profound qualitative differences in absorption between the large and small intestines. Under normal conditions no food substances are absorbed from the large intestine not because it is impossible, but because the chyme contains no absorbable substances by the time it reaches the large intestine. At the same time it has long been known that very considerable amounts of water can be absorbed from the large intestine—the liquid content of the upper division of the large intestine condenses on the way to the rectum. Under normal conditions the peristaltic and antiperistaltic movements of the large intestine maintain a high hydrostatic pressure for a long time, which aids in the passage of the water into the blood. A number of substances diffuse in large amounts from the blood into the small intestine; upon entering the large intestine these substances are reabsorbed and are thus returned to the organism.

Upon reaching the large intestine, glucose, fat and fatty acids are absorbed there, though slower than in the small intestine. Hence, it is clear that nutritive enemas are of real importance to feeding. In this case a certain role can be played by the enzymes which pass into the large intestine from the small intestine or which are formed by microorganisms; for example, they can split up dextrin, peptones and other substances.

PART VII

METABOLISM AND VITAMINS

CHAPTER 31

METABOLISM

General Ideas of Metabolism

Life is inseparably connected with assimilation of various organic and inorganic substances from the environment and excretion of the waste or superfluous matter, in particular the break-down products of the substances consumed, into the environment. Thus, the body constantly exchanges substances with its external environment. The exchange of substances (metabolism) is an inalienable sign of life. The energy required for maintaining the temperature of the animal's body on a certain level, for muscular work, for synthesizing various compounds and overcoming the osmotic forces during the secretory and excretory processes, for various electrical phenomena, etc., is produced by the transformation and oxidation of complex organic compounds which form part of the tissues. This aspect of metabolism is designated as *catabolism* or ***dissimilation.*** At the same time all tissues of the organism are constantly renewed, restored and rebuilt. This part of metabolism is known as ***anabolism*** or *assimilation.* In metabolism assimilation and dissimilation are indissolubly connected. During the process of assimilation, when organic substances are synthesized, there are simultaneous other reactions which lead to disintegration and oxidation—to CO_2 and water—of other organic substances. The synthesis of complex organic compounds in the body is preceded by the formation of low molecular products. Thus, for example, the synthesis of protein bodies, which is effected at the expense of other proteins, is preceded by hydrolysis of the latter to amino acids.

Contrariwise, in the process of disintegration many substances go through synthesis which produces substances more complex than the initial substance. Thus, in order to break up, glucose must necessarily be phosphorylated and form hexosephosphates. The oxidative disintegration of acetic acid is effected through its combination with oxalo-acetic acid and the formation of citric acid, a hexacarbon compound.

A detailed consideration of the physicochemical basis of the metabolic processes and a description of the transformations of the various substances in the organism are the subject matter of a course in biochemistry. Below we give only essential information on the fate of nutritive substances in the organism and on the physiological significance of the different processes of metabolism.

Carbohydrate Metabolism

Carbohydrate requirements. Of the substances compensating man for his energy output in an ordinary diet carbohydrates are of the greatest importance. In moderate muscular work man requires about 500 gr. of carbohydrates per day. The nutritive carbohydrates are starch, cane sugar, lactose, maltose, glucose, fructose and glycogen. In the digestive tract the polysaccharides (starch and glycogen) and the disaccharides (saccharose, lactose and maltose) are converted to monosaccharides and the latter are absorbed into the blood from the small intestine.

Glycogen of the liver. The monosaccharides, which enter the blood from the intestines, pass through the system into the liver where they are transsformed into glycogen—a polysaccharide composed of a large number of glucose particles. As Claude Bernard demonstrated for the first time (1852) that the liver played the part of a carbohydrate depot forming glycogen from the absorbed glucose and storing it. As the body uses up the carbohydrates the glycogen of the liver changes to sugar, enters the blood and is carried by it throughout the system.

In addition to monosaccharides many other substances brought by the blood—lactic acid, glycerol and various amino acids—can also be utilized by the liver for synthesizing glycogen. This has been established in experiments both on the isolated liver and on the body as a whole. Experiments on dogs poisoned by phloridzin proved very useful in solving this problem. These dogs lose a large amount of sugar with the urine (phloridzin glycosuria) and mobilize all resources by means of which sugar and glycogen can be formed in order to maintain the necessary concentration of sugar in the blood. By feeding the dogs protein food or amino acids and analysing later the relation between the sugar and nitrogen excreted with the urine it is possible to ascertain what part of the total quantity of carbon atoms of the protein or the amino-acids makes up the sugar. It has been found that an average of approximately 56 gr. of sugar can be formed from 100 gr. of protein.

When large amounts of carbohydrates are consumed with the food the glycogen content in the liver may exceed 10 per cent of its weight. Under normal dietary conditions the amount of glycogen in the liver of man constitutes about 150 gr. Though, in addition to the liver, glycogen is also stored in the muscles, the nerve cells and other tissues, only the liver glycogen reserve is used for the needs of the body as a whole.

The vitally important role of the production and accumulation of glycogen reserves in the liver is well demonstrated in experiments in which the liver is removed. In these experiments the animal dies very quickly—in 2 to 3 hours. Introduction of glucose into the blood of such an animal sharply improves its condition for some time. When the injected glucose is utilized by the organism and the sugar content in the blood drops again the condition of the animal becomes worse again. By repeated injections of glucose it is possible to keep the hepatectomized animal alive for 12 to 16 hours, after which it dies of other pernicious results produced by the removal of the liver (p. 319).

Sugar content of the blood. On an empty stomach the blood of man contains 70 to 100 mg. per cent (0.07 to 0.1 per cent) sugar. When large amounts of carbohydrates are consumed with the food the content of sugar in the blood increases because the liver has no time to transform all of the absorbed sugar into glycogen. The increase in the content of glucose in the blood (*hyperglycaemia*) is the more pronounced the faster the sugar is absorbed from the intestines. In sharply pronounced *alimentary* hyperglycaemia (150 to 180 mg. per cent sugar in the blood) sugar begins to be excreted with the urine (*glycosuria*). The maximal amount of sugar consumed without signs of glycosuria may serve as the measure of the functional capacity of the liver as regards glycogen production. The maximal amounts of sugar which do not cause glycosuria in healthy people when taken at one time are 150 to 180 gr. of glucose, 150 to 200 gr. of cane sugar, 120 to 150 gr. of fructose, and 40 gr. of galactose.

In diabetes mellitus, a disease caused by a derangement in carbohydrate metabolism, the concentration of sugar in the blood may reach very high figures (up to 500 mg. per cent) and the amount of sugar lost with the urine runs into scores and even hundreds of grams.

Under certain conditions (long and hard muscular work, injection of insulin) the concentration of sugar in the blood drops; this condition is known as *hypoglycaemia*.

Intermediate carbohydrate metabolism. Carried throughout the organism by the blood glucose enters the different organs, muscles, the brain and the glands. In these organs the glucose is either directly utilized (for example, in the brain), first changed into glycogen (in muscles and most other organs) or transformed into other sugars (for example, into lactose during the production of milk in the mammary glands).

The muscles contain 0.4 to 1 per cent glycogen. The hydrolysis of glycogen and the oxidation of the intermediate metabolites are the principal chemical process which provide the energy for muscular work. Phosphoric compounds (inorganic phosphates, adenyl system, codehydrase) must necessarily take part in this process. They are also involved in the production of phosphoric esters—hexose and triose. Under anaerobic conditions the reactions stop at the lactic acid stage. As a result of the transformations of glycogen into lactic acid (glycogenolysis) the adenyl system is enriched by phosphate groups and adenosine triphosphoric acid is formed. The latter contains two phosphate radicals whose liberation releases a large amount of energy (about 10 large calories per gram-molecule of the liberated phosphoric acid). It is apparently this energy that is used for muscular contraction, while glycogenolysis serves only to restore the adenosine triphosphoric acid.

Lactic acid does not accumulate in the presence of oxygen, and the intermediate products of carbohydrate metabolism are oxidized to carbon dioxide and water. The oxidative processes also involve phosphoric compounds and phosphate groups which form part of adenosine triphosphoric acid. Much more energy is liberated during the oxidation of glycogen than during its anaerobic transformation into lactic acid.

Cerebral tissue uses glucose as the basic carbohydrate substance. The normal function of the central nervous system is possible only when it receives sufficient glucose from the blood. A sharp drop in sugar concentration in the blood causes convulsions and death (*hypoglycaemic shock*).

Regulation of carbohydrate metabolism. Depending on the conditions of the organism's existence and on the influences of the environment the carbohydrate metabolism of the organism as a whole or in its individual organs may vary considerably. For example, in muscular work the consumption of carbohydrates sharply increases.

During muscular contractions the rate of glycogenolysis and of lactic acid production in the muscles is hundreds of times as high as at rest. If the amount of oxygen brought by the blood to the working muscles is not enough to oxidize the lactic acid the latter accumulates in the muscles and passes into the blood. Lactic acid also accumulates when the tissues are not supplied with sufficient oxygen (in a rarefied atmosphere, disorders of respiratory and circulatory functions, etc.). When the tissues get enough oxygen the processes of glycogenolysis and glycolysis are, on the contrary, inhibited (Pasteur effect) while the lactic acid, which has formed, is partly oxidized and partly reconverted into glycogen.

Carbohydrate metabolism is regulated by the nervous system involving certain endocrine glands which are themselves under the control of the nervous system. The importance of the nervous system in the regulation of the sugar concentration in the blood was already demonstrated by Claude Bernard.

A puncture in the floor of the IV ventricle of the rabit's medulla oblongata causes mobilization of the liver glycogen and sharply increases the content of sugar in the blood, with sugar appearing in the urine (nervous or puncture glycosuria).

Stimulation of the floor of the IV ventricle influences the hepatic cells through the sympathetic nerves and, what is in this case more important, via the neurohumoral channel. Stimulation of the nervous centres through the sympathetic nerves causes an increased production of adrenalin by the medulla of the adrenals. Adrenalin enters the blood and, brought to the liver, aids in the conversion of glycogen to sugar and, consequently, produces hyperglycaemia.

Insulin, the hormone formed in the pancreas by the islands of Langerhans, produces an opposite effect on the concentration of blood sugar. Insulin aids in the conversion of sugar to glycogen and in the utilization of sugar with the formation of the intermediate products of its metabolism. Introduction of insulin causes the concentration of sugar in the blood to drop.

The third hormone involved in carbohydrate metabolism is one of the substances formed in the anterior lobe of the hypophysis (the hormone of growth). This hormone depresses the phosphorylation reaction of glucose, the very first reaction in sugar conversion. The hormones produced by the cortical part of the adrenals also, undoubtedly, influence carbohydrate metabolism, though this influence is not sufficiently clear.

The functions of all these endocrine glands are under the control of the nervous system which, in the final analysis, regulates the entire carbohydrate metabolism.

The cerebral cortex plays the most important part in the nervous regulation of carbohydrate metabolism in higher animals. The ingestion of a sugar solution increases metabolism in man and animals by the direct action of the sugar on the tissues (specific-dynamic action of carbohydrates). If, however, the sugar intake is repeatedly combined with a sound stimulus the action of the sound stimulus alone will cause nearly the same increase in metabolism and in the sugar concentration in the blood as does the ingestion of sugar. Thus, any stimulus, any influence of the external environment, combined with the agents which directly produce changes in carbohydrate metabolism may become the stimulator or inhibitor of particular metabolic processes through the cerebral cortex.

The influence of the cerebral cortex is also manifested in the fact that under emotional stress (fright, anxiety, anger) the concentration of sugar in the blood sharply increases. It is also possible to cause alterations in the concentration of sugar in the blood by suggestion in hypnosis.

Carbohydrate metabolism cannot be considered apart from the metabolism of proteins and fats. The metabolic processes in the organism involve an interrelation and interweaving of various forms of metabolism. It has already been said that proteins and even fats may become the sources for the formation of glycogen. Contrariwise, fats may be extensively formed from carbohydrates, which is actually the case when animals are fattened. Certain amino acids can also be formed from carbohydrates by reamination (transfer of amino-groups from some substances to others).

The relationship between the intermediate metabolism of carbohydrates and fats is clearly manifested in diabetes mellitus, a disease in which the utilization of carbohydrates is deranged, the concentration of sugar in the blood is increased and the sugar begins to pass into the urine. In this case inadequate utilization of carbohydrates and the derangement in their intermediate metabolism leads to an impairment of the metabolism of fats, which consists in an accumulation of harmful products of fat metabolism—ketone bodies (acetone, acetoacetic acid and beta-oxybutyric acid). In the organism carbohydrates produce an *antiketogenic* effect by reducing the formation of ketone bodies.

Metabolism of Fats and Lipoids

Physiological significance of fats and lipoids. Fats and lipoids (fatty substances) are indispensable constituents of cellular bodies in which they are found either as parts of the protoplasm or as constituents of the cellular structures. Some tissues, for example nervous tissues and the adrenals, are particularly rich in lipoids. The properties of the cell membranes show that they also contain lipoids. Reserve fat consisting mainly of triglycerides of fatty acids may accumulate in considerable quantities in loose connective tissue—in subcutaneous cellular tissue, in the epiploon and in the cellular tissue surrounding the internal organs. The total amount of fat in the organism constitutes 10 to 20 per cent and in cases of obesity even much more.

Fats play the part of reserve nutritive material. In addition, the fatty cellular tissue serves as a bed for a number of internal organs and aids in holding them in place. Subcutaneous fatty cellular tissue plays a protective role and serves as a thermal insulation material. Certain unsaturated fatty acids (linolic acid, arachidonic acid) are not synthesized by the higher animals, but are indispensable to the nutrition of man and animals.

Lipoids may be divided into two basic groups. The first group consists of *phospholipids* or *phosphatides* which in addition to particles of polyatomic alcohol and fatty acids also contain in their molecules phosphoric acid and a nitrogenous base (for example, choline in lecithin or sphingomyelin, and ethylamine in cephalin). The phospholipids are a plastic material forming part of all tissues. Their content is particularly high in brain tissue.

Sterols, the other group of lipoids, have an entirely different structure from that of the fats. Cholesterol, the chief representative of this group, has a cyclical structure consisting of three six-member and one five-member rings, a long side chain, one double bond in chain B and a hydroxyl group in ring A. The last group lends cholesterol the properties of a monoatomic secondary alcohol. As an alcohol cholesterol in combination with fatty acids (palmitic acid, etc.) yields esters. In the cells and tissue fluids cholesterol is found in a free state and in the form of esters. The content of cholesterol is particularly high in the brain.

Metabolism of fats. Under normal working conditions man requires 50 to 60 gr. of fat per day.

The fats entering the digestive tract are hydrolyzed and absorbed. If a large amount of fats is consumed with the food their concentration in the blood plasma may increase from a few tenths of one per cent (0.3 to 0.4) to one per cent and more (*lipaemia*). During the synthesis of fat in the intestinal wall after absorption and when fat is deposited as a reserve nutritive material it is rebuilt. Alien fat is changed to fat with a composition characteristic of the given animal.

In their physical properties, particularly in the melting point, the fats of various animals considerably differ from each other. But even in the same animal the fats taken from different parts of the body differ in their physicochemical properties; they have different melting points, refraction indices, content of unsaturated fatty acids, etc. The composition of an animal's fat is influenced by factors of the external environment. If a starved animal be fed a large amount of fats which sharply differ in composition from its own fat the body of the animal will show traces of fats in composition approximating the food fat. The composition of fats is also influenced by the temperature conditions under which the animals are kept.

Other nutritive substances, besides food fats, serve as sources of fat in the body. Fats can be synthesized from carbohydrates and from proteins. The initial substances for this are the intermediate products of metabolism common to carbohydrates, proteins and fats—pyruvic acid, acetic acid and some other substances.

Intermediate metabolism of fats. In the course of the intermediate metabolism of fats glycerol is easily converted into glycogen or its intermediate metabolites. The fatty acids are oxidized. The first products of oxidation are the beta-oxyacids, then come the beta-keto-acids; the beta-keto-acids are split up, the remnant of acetic acid is removed and the carbon chain of the initial fatty acid is shortened by two carbon atoms.

The acetic acid thus formed is further drawn into a cycle of chemical conversions (the citric acid cycle) accompanied by its oxidation to carbon dioxide and water.

As in the oxidation of carbohydrates the oxidation conversions of the fatty acids draw inorganic phosphorus into the composition of adenosine triphosphoric acid which is a universal power-producing substance. It has been shown that muscles can work not only by consuming glycogen, but also by oxidizing fatty acids.

The intracellular metabolism of fats is closely connected with the intermediate metabolism of carbohydrates (in particular, in the citric acid cycle) and is impaired in disorders of the latter. If the acetic acid is not drawn into the citric acid cycle in sufficient quantities it is transformed into acetone or ketone bodies (acetoacetic acid, acetone, beta-oxybutyric acid). It is the formation of these bodies that is, probably, responsible for the serious poisoning in grave diabetes and death, when the accumulation of ketone bodies in the blood increases to an enormous extent. Part of them are voided with the urine (*acetonuria*). Ketone bodies accumulate when the reserve of carbohydrates in the organism is limited (in starvation, consumption of foods rich in fats, after long hard work).

The ability of carbohydrates to prevent the accumulation of ketone bodies is called *antiketogenic* action.

The metabolism of fats like that of carbohydrates is influenced by the nervous system. This is confirmed by a number of data. For example, by injuring the hypothalamus it is possible experimentally to make the animal grow fat. Of the endocrine glands the metabolism of fat is regulated by the hypophysis, the sexual glands, the thyroid, the pancreas and the adrenals whose functions are also regulated by the central nervous system. The anterior lobe of the hypophysis produces a hormone which fosters the accumulation of ketone bodies in the organism. In disorders of the internal secretion of the sexual glands obesity, which acquires pathological forms, is sometimes observed. Insufficient formation of the so-called *lipocaic* substance in the pancreas results in a fatty infiltration of the liver.

Metabolism of lipoids. Studies with the use of artificial radioactive phosphorus have shown that the liver is the place where phospholipids are newly formed and where their intensive metabolism takes place. The synthesis of such a phospholipid as lecithin requires a sufficient amount of choline which forms part of it. Though choline can be synthesized in the body at the expense of oxyethylamine and methionine (amino acid) the limited amount of the latter in proteins makes it necessary to introduce choline directly into the food. Insufficient choline in the food results in a fatty infiltration of the liver. Choline is, therefore, sometimes considered a vitamin.

The phospholipids, which form part of the brain tissue, are rebuilt and renewed, though much slower than those of the liver (G. Vladimirov et al.). The white matter of the brain contains considerable quantities of cerebrosides which closely resemble sphingomyelin (phospholipid). The cerebrosides contain galactose but no phosphoric acid or choline.

Of sterol only those of animal origin—cholesterol and dehydrocholesterol—are absorbed. Cholesterol is easily synthesized in the animal organism and is excreted with the bile and through the mucosa of the large intestine. In the large intestine cholesterol is reduced to coprosterol by the action of bacteria and in this form becomes part of the faeces. Among the steroids, substances chemically close to cholesterol, there are many very active substances (cortical hormones, sexual hormones, provitamins D, bile acids). Certain vegetable heart poisons (strophanthin and digitonin), the poison of the toad (bufotoxin) and, finally, substances which cause the formation of malignant tumours (so-called cancerogenic substances) contain steroid groups or are close to steroids in their chemical structure.

The carotenoids also belong to fat-like substances. Some of them (carotene, xanthophyll, etc.) serve as the sources for the formation of vitamin A. In addition to vitamin A, vitamin E and vitamin K are also fat-soluble vitamins. Like fats they can be absorbed only in the presence of bile in the intestines.

Metabolism of Proteins

Biological significance and specificity of proteins. Proteins are the essential substance of which the protoplasm of the cells and the intercellular substances are built. All the enzymes without which the metabolic processes cannot take place are protein bodies. The phenomena of muscular contraction are connected with proteins—myosin and actin. The carriers of oxygen in the blood are pigments of a protein nature—haemoglobin in higher animals, and chlorocruorin and haemocyanin in lower animals. The blood owes its ability to coagulate to the plasma protein—fibrinogen.

The immunity properties of the organism are connected with certain substances of the plasma. the so-called antibodies. One of the protein substances of the retina—visual purple or rhodopsin—increases the sensitivity of the retina to light. The nuclear and cytoplasmic nucleoproteids play an essential part in the processes of growth and reproduction. The phenomena of excitation and its propagation are connected with protein bodies. The hormones, which take part in regulating physiological functions, contain a number of protein substances.

Proteins have a very complex structure. Converted by acids, alkalis and proteolytic enzymes protein splits to amino acids of which there are more than 25. In addition to amino acids different proteins contain many other constituents (phosphoric acid, carbohydrate groups, lipoid groups and special groups).

Proteins are highly specific. Each organism and each tissue have proteins which differ from those that form part of other organisms and other tissues. The high specificity of proteins can be ascertained by the following biological test. If a vegetable protein or a protein from a different animal is injected into the blood of an animal the organism responds by a general reaction consisting in a change of function of a number of organs and a rise in temperature. At the same time special protective enzymes, capable of converting the alien protein introduced, are formed in the organism.

Parenteral (i.e.. other than the gastrointestinal tract) introduction of an alien protein after the lapse of a certain time renders the animal extraordinarily sensitive to the repeated introduction of this protein. Thus, if the guinea-pig is administered a small amount (1 mg. or even less) of an alien protein (serum proteins of other animals, egg proteins, etc.) parenterally the repeated injection of a few milligrams of the same protein 10 to 12 days later (incubation period) causes a stormy reaction in the guinea-pig. The reaction manifests itself in convulsions, vomiting, intestinal haemorrhages, drop in blood pressure, respiratory disorders and paralysis. The animal may die as a result of these disorders. This increased sensitivity to alien protein has been named *anaphylaxis* (C. Richet, 1902), while the aforesaid reaction of the organism is referred to as an *anaphylactic shock*. A much greater dose of an alien protein administered the first time or before the end of the incubation period does not cause an anaphylactic shock. The increase in sensitivity of an organism to any particular influence is called ***sensibilization***. The sensibilization of the organism caused by a parenteral administration of an alien protein is retained for many months and even years. It can be eliminated by repeated injections of the same protein before the end of the incubation period.

The anaphylactic phenomenon is also observed in man in the form of the so-called "serum disease" after repeated introduction of therapeutic serums.

The high specificity of proteins is understandable if we consider that various combinations of amino acids make possible the formation of an endless number of proteins with different combinations of amino acids. The hydrolysis of proteins in the intestines not only ensures the possibility of their absorption but also provides the organism with materials for the synthesis of its own specific proteins.

The main significance of proteins is that they furnish the material from which the cells and intercellular substance are built and the substances, which take part in the regulation of physiological functions, are synthesized. However, proteins are in some measure used along with carbohydrates and fats to cover the energy output.

Intermediate metabolism of proteins. In the alimentary canal proteins are converted by proteolytic enzymes (pepsin, trypsin, chemotrypsin, polypeptidases and dipeptidases) into amino acids. Passing into the blood from the intestines the amino acids are carried throughout the body, and proteins are synthesized from them in the tissues.

The studies with the heavy isotope of nitrogen (N^{15}) have shown that protein bodies are constantly rebuilt in the organism with amino acids leaving and re-entering their composition. The proteins of the body are in a state of continuous exchange with the amino acids which are in the composition of the nonprotein fraction. Some amino acids are also converted into others in the body. These conversions include reamination. which consists in the transfer of amino-groups from amino acids to keto-acids (A. Braunshtein and M. Kritsman). In the oxidative disintegration of amino acids deamination occurs first. Ammonia, which is split off as one of the end products of protein metabolism, is further converted largely into urea in higher animals. In man the nitrogen in urea constitutes an average of 85 per cent of the total nitrogen of the urine.

The principal end product of protein metabolism in birds and reptiles is not urea, but uric acid. Even the urea introduced into the organism of birds is converted into uric acid. This peculiarity in nitrogen metabolism is connected with the fact that the embryonic period in the life of birds takes place in an enclosed space, within the egg. Uric acid has very low solubility and does not easily penetrate through animal membranes. The accumulation of such a product of nitrogen metabolism as uric acid in the cavity of the allantois and embryos does not, therefore, harm the embryos.

In mammals uric acid is formed only from purine bodies which are part of nucleoproteides and nucleotides; the latter are coenzymes of certain fermentative systems.

In dogs uric acid is further converted, and allantoin is the end product of the metabolism of purine bodies.

The important end products of nitrogen metabolism also include creatinine and hippuric acid. Creatinine is an anhydride of creatine. Creatine is found in the muscles and in brain tissue in a free state and in combination with phosphoric acid (phosphocreatine).

Creatinine is formed from phosphocreatinine by liberation of phosphoric acid. The amount of creatinine voided with the urine is relatively constant (1.5 gr. per day) and hardly depends on the quantity of proteins taken in with the food. Only when meat food rich in creatine is consumed does the amount of creatinine in the urine increase.

Hippuric acid is synthesized from benzoic acid and glycocoll (in dogs mainly in the kidneys, in most of the animals and in man—in the liver and, to a lesser extent, in the kidneys).

This synthesis is, apparently, aimed at rendering the benzoic acid harmless. Particularly large quantities of hippuric acid are formed in herbivorous animals owing to the fact that vegetable food contains substances which in the animal organism are converted into benzoic acid. An increase in hippuric acid is observed in the urine of man when the latter changes to a vegetable diet.

Amines (for example, histamine) are products of protein conversion and are sometimes of great physiological importance.

Role of liver and kidneys in protein metabolism. When the blood flows through the liver amino acids are partly retained and a "reserve" protein, which can be easily utilized by the body during limited protein consumption, is synthesized from them in the liver. A small reserve of protein can, apparently, also be stored in the muscles (A. Danilevsky).

Proteins are probably also formed in the liver. Thus, after a loss of blood the normal concentration of albumins and globulins in the blood plasma is rapidly restored. But if the function of the liver is impaired by phosphoric poisoning the restoration of the normal protein composition of the blood is greatly impeded. The formation of albumins in the liver has been demonstrated in experiments with its finely ground tissue. The liver also plays the leading part in intermediate protein metabolism. Processes of deaminization and the synthesis of urea take place in the liver on a large scale. A number of toxic products of intestinal putrefaction of proteins (phenols, indol) are also rendered harmless in the liver. Removal of the liver causes the animal to die some time later even if glucose is repeatedly introduced. This is, apparently, due to poisoning with the products of the intermediate protein metabolism, in particular, accumulation of ammonia. An important part in the study of the functions of the liver was played by the method of vein-to-vein anastomosis (Eck-Pavlov fistula).

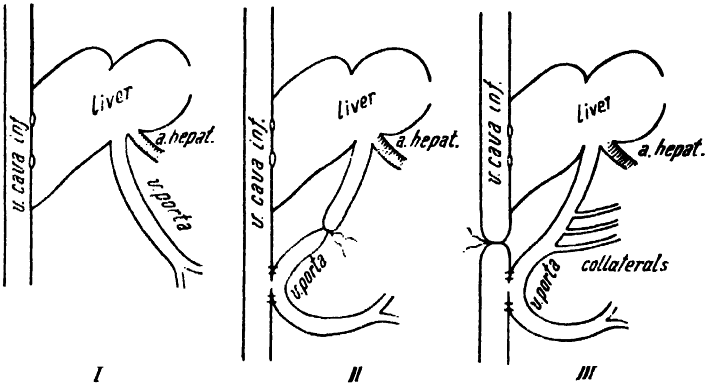

Fig. 134. Diagram of Eck-Pavlov fistula.

I — diagram of vessels before operation; *II* — Eck-Pavlov fistula. Anastomosis between portal vein and inferior vena cava; portal vein tied off between the anastomosis and liver; *III* — "inverted" Eck-Pavlov fistula. After placing anastomosis between portal vein and inferior vena cava, the latter is ligated above the anastomosis in which case collaterals develop between portal and azygos veins.

The Eck-Pavlov fistula is formed by anastomosing the portal vein and the inferior vena cava (Fig. 134) with a portion of the portal vein near the liver tied off. As a result of this operation the blood flowing away from the intestines and passing into the portal vein cannot enter the liver, but by-passes it and empties into the inferior vena cava. This operation preserves the vital capacity of the liver since the latter is supplied with blood through the hepatic artery. But this makes it impossible for the liver to retain the toxic substances absorbed by the intestines. This difficult operation was performed by N. Eck for the first time in I. Tarakhanov's laboratory. However, Eck was unable to keep the dogs with such fistulas alive. In 1892 I. Pavlov operated on about 60 dogs, close to a third of which remained alive and was studied. M. Nentsky and his associates did the biochemical part of the studies. It turned out that the dogs with the Eck-Pavlov fistulas could live for a considerable time if their food contained little protein. With protein feeding, especially if the dogs are given a large amount of meat, they are poisoned by the toxic products of protein conversion. The animal becomes excited, the coordination of movements is affected, it is seized by convulsions and dies. An increased ammonia concentration in the blood is observed.

The kidneys play an important part in the metabolism of proteins. In the kidneys ammonia is liberated from the amino acids and is used for neutralizing the acids. The latter are voided with the urine in the form of ammonium salts.

It is through the kidneys that the body rids itself of the nitrogenous end products of protein metabolism (urea, creatinine, uric acid, hippuric acid and ammonia). When the functions of the kidneys are impaired as a result of disease all these products are retained in the tissues and in the blood; this leads to an accumulation of nonprotein (so-called *residual)* nitrogen in the blood (uraemia). An increased accumulation of nitrogenous products of metabolism in the blood leads to death.

Metabolism of complex proteins. The nucleoproteids take part in growth and reproduction. In tissues, which no longer increase their mass, the role of nucleoproteids is. apparently, confined to participation in reproduction of the protein substances of the tissues. The metabolism of cytoplasmic nucleoproteids (ribonucleoproteids) proceeds more vigorously than that of the nuclear nucleoproteids (desoxyribonucleoproteids). Thus, the rate of renewal of phosphorus in the ribonucleic acid of the liver is 30 times as high, and in the ribonucleic acid of the brain 10 times as high as in the desoxyribonucleic acid of the same tissues. The metabolism of nucleoproteids in the human organism is determined by the excretion of purine bodies, particularly uric acid, 0.7 gr. of which is excreted per day under normal dietary conditions. More of it forms in the organism on a meat diet. In metabolic disorders manifesting themselves, for example in *gout*, the uric acid, which dissolves with difficulty, is stored in the tissues, particularly around the joints.

Haemoglobin constantly breaks up and is resynthesized in the body. Glycocoll and acetic acid are used in the synthesis of the haemin group. A sufficient intake of iron is also necessary.

The intensity of haemoglobin disintegration in the body can be judged by the formation of bile pigments whose appearance is connected with the splitting of the porphyrin ring of the haemin group and the liberation of iron. The bile pigments pass with the bile into the intestines and are reduced in the large intestine to *stercobilinogen* or *urobilinogen*. Part of the urobilinogen is lost with the faeces; the rest is absorbed from the large intestine and gets into the liver whence it passes into the bile again. In certain ailments of the liver urobilinogen is not fully retained in the liver and passes into the urine. In the presence of oxygen in the urine urobilinogen is oxidized into urobilin owing to which the urine turns dark.

Balance of nitrogen metabolism. The study of the metabolism of proteins is facilitated by the fact that proteins contain nitrogen. Different proteins contain from 14 to 19 per cent nitrogen, the average being 16 per cent. Each 16 gr. of nitrogen correspond to 100 gr. of protein; one gram of nitrogen, consequently, corresponds to 6.25 gr. of protein. Therefore, in studying the *nitrogen balance*, i.e., the amount of nitrogen taken in with the food and the amount of nitrogen excreted by the organism, it is possible summarily to characterize the metabolism of protein. The assimilation of nitrogen by the organism equals the nitrogen of the food minus the nitrogen of the faeces; the elimination equals the amount of nitrogen excreted with the urine. By multiplying the amounts of nitrogen by 6.25 we determine the quantity of the consumed and disintegrated protein. The accuracy of this method is affected by the organism's losses of proteins from the skin surface (the desquamation of cells of the corneous layer of the epidermis, growing hair and nails). The process of protein conversion in the organism and the elimination of the products of metabolism, like the assimilation of the absorbed proteins, require many hours. In order to determine the value of protein disintegration in the organism it is, therefore, necessary to collect the urine for a period of a day, and in important studies—even for many days running.

During the growth of the body or during its increase in weight owing to the assimilation of greater amounts of proteins (for example, after starvation, after infectious diseases, etc.) the amount of nitrogen taken in with the food is larger than that which is excreted. The nitrogen is retained in the body in the form of a protein nitrogen. This is designated as the *positive nitrogen balance*. In starvation or in ailments, which are attended by a high disintegration of proteins, more nitrogen is excreted than consumed, and this is referred to as the *negative nitrogen balance*. When the quantities of nitrogen consumed and excreted are equal we speak of *nitrogen equilibrium*.

The metabolism of proteins essentially differs from that of fats and carbohydrates in that in the healthy adult hardly any of the easily utilized reserve protein is stored. The amount of reserve protein stored in the liver is insignificant and it is not retained for any length of time. An increase in the total mass of proteins in the body is observed only during the period of growth, during recovery from infectious diseases or starvation and, to a certain extent, during intensive muscular training when there is an increase in the total mass of muscles. In all other cases an excessive intake of protein causes its greater disintegration.

Therefore, if a person in a state of nitrogen equilibrium begins to consume large amounts of proteins with his food the amount of nitrogen excreted with the urine will also increase. But it takes several days to establish a state of nitrogen equilibrium on a higher level. The same occurs in the reverse order, in passing to a lower level of nitrogen equilibrium. As the quantity of nitrogen taken in with the food decreases the amount of nitrogen excreted with the urine also diminishes and within a few days equilibrium is established on a lower level.

Under normal dietary conditions the nitrogen equilibrium is established when 14 to 18 gr. of nitrogen is excreted with the urine. If the amount of proteins in the food decreases it can also be established at 8 to 10 gr. A further reduction in the quantity of proteins in the food results in a negative nitrogen balance. The minimum of protein nitrogen (6 to 7 gr.) taken in with the food and still permitting nitrogen equilibrium to be maintained is called the *protein minimum*. The amount of nitrogen excreted with the urine during protein starvation depends on whether or not other nutritive substances are consumed. If all of the energy outlays of the body can be covered at the expense of other nutritive substances the amount of nitrogen excreted with the urine can be reduced to 1 gr. per day and even lower.

If the body receives less proteins than the protein minimum it experiences protein hunger: the body does not sufficiently make up for the protein losses. Depending on the extent of starvation the negative nitrogen balance holds out no danger to the organism for some time. Observations of "marathon fasters," who took no food but only small amounts of water for periods of 20 to 50 days, have been described. However, continued starvation leads to death.

In total starvation for a long time the amount of nitrogen excreted sharply decreases during the first days, but is later maintained on a constant low level (Fig. 135). Experiments on animals have shown that shortly before death the nitrogen disintegration in the organism increases again. This is due to the exhaustion of the last remnants of other energy resources, particularly fats.

Protein requirements in the diet. Owing to the fact that under different dietary conditions the minimum may vary, while the significance of large quantities of proteins in the food is not clear as yet, the protein requirements have not been definitely established. Proceeding from statistical figures Voit proposed 118 gr. of protein as a daily norm. The norms fixed by Chittenden (35 to 60 gr.) are absolutely insufficient, as numerous observations have shown, and as a rule result in a negative nitrogen balance.

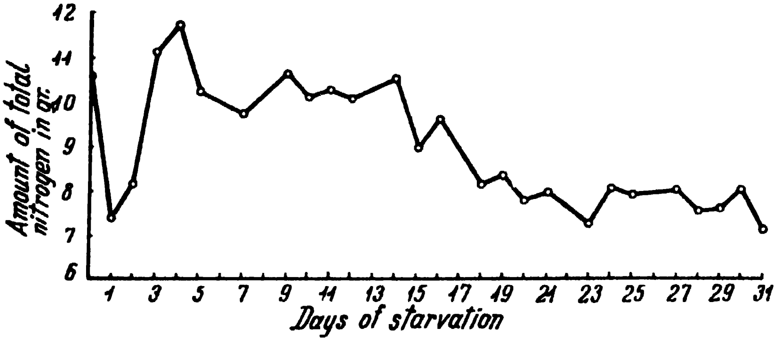

Fig. 135. Influence of complete starvation on daily total output of nitrogen in urine (after Benedict).

The studies of Soviet scientists (O. Molchanov et al) warrant the assumption that 100 to 120 gr. of proteins per day is the best-founded minimum. Consumption of greater amounts of proteins does not harm healthy people.

It should be borne in mind that the quantitative requirements in protein food retain their significance only on the condition that the food proteins are of the requisite composition. A number of amino acids, whose synthesis is entirely impossible in the animal body, must necessarily be included in the food in order to ensure the synthesis of the body's proteins. On the contrary, certain amino acids can be synthesized from other amino acids and even from non-nitrogen bodies and ammonia, and they do not have to be consumed with food. Recent investigations have shown that the number of such amino acids is greater than was formerly believed.

Of the 20 amino acids cited below only 8 are of vital importance to man.

Essential amino acids	Nonessential amino acids	
Valine	Glycocoll	Glutamic acid
Leucine	Alanine	Tyrosine
Isoleucine	Citrulline	Proline
Lysine	Serine	Hydroxyproline
Methionine	Cystine	Arginine
Threonine	Aspartic acid	Histidine
Phenylalanine		
Tryptophane		

If the food lacks one of these essential amino acids the processes of protein synthesis in the organism are deranged. Growth in the growing organism is retarded and followed by a loss of weight. Thus, the "law of minimum" is applicable to the protein diet because the synthesis of protein in the organism is limited by the essential amino acid which is consumed with the food in minimal amounts.

The proteins containing the necessary amino acids in proportions most favourable for the synthesis of proteins in the body are most fully utilized by it. It appears, therefore, that the maintenance of the animal's normal growth requires unequal amounts of different proteins, i.e., the biological value of the proteins depends on their amino acid composition and is unequal. The biological value of proteins is measured by the amount of the protein of the body that can be formed from 100 gr. of the food protein. It seems that animal proteins (meat, eggs and milk) have a high biological value (70 to 95 per cent), while most of the vegetable proteins (rye bread, oats, maize) have a lower biological value (60 to 65 per cent). There are, however, also animal proteins (for example, gelatin) which do not contain certain valuable amino acids (tryptophane, tyrosine, cystine) and are, therefore, inferior.

Regulation of protein metabolism. The intensity of protein metabolism depends in large measure on the humoral influences of the thyroid gland. *Thyroxin*, the hormone of the thyroid gland, increases the intensity of the protein metabolism. In Basedow's disease, which is characterized by an increased secretion of the thyroid hormones (hyperthyroidism), the protein metabolism is increased. Contrariwise, during hypofunction of the thyroid gland (hypothyroidism) protein metabolism sharply decreases. Since the function of the thyroid gland is under the control of the nervous system the latter is the real regulator of protein metabolism (p. 421).

The nature of the consumed food exerts considerable influence on the metabolism of proteins. Meat food gives rise to greater amounts of uric acid, creatinine and ammonia. Vegetable food produces much smaller quantities of these substances because it contains little of the purine bodies and creatine. The amount of ammonia formed in the kidneys depends on the acid-base balance in the body; more of it is formed in acidosis, less in alkalosis. With vegetable food the organism takes in a considerable amount of alkaline salts of organic acids. Organic acids are oxidized to carbon dioxide which is eliminated through the lungs. The coresponding part of the base remaining in the organism and later excreted with the urine shifts the acid-base balance towards alkalosis. Vegetable food does not, therefore, require the formation of ammonia in the kidneys for the neutralization of the surplus of acids and in this case the urine contains very little of it.

CHAPTER 32

VITAMINS

Discovery of Vitamins and Methods Used in Their Study

Two ways led to the development of the vitamin doctrine. One of them was connected with the attempts to make up a healthful diet of proteins, fats and carbohydrates free of admixtures. It had been known since the time of Liebig (middle of the 19th century) that proteins, fats, carbohydrates and salts were necessary constituents of food. In his thesis submitted at Yuriev University (1880) N. Lunin proved by experiments performed on mice that in addition to these nutritive substances some other substances contained in milk were absolutely necessary for the maintenance of life. Lunin's discovery was later confirmed and developed by Russian and foreign scientists (Pashutin, Hopkins, McCollum, Funk et al).

On the other hand, mankind has suffered since time immemorial from serious diseases which affected people living on an inferior, monotonous diet.

We know from the history of wars, since the Crusades, that food deficient in meat and fresh vegetables resulted in a mass incidence of scurvy. Scurvy was also the bane of seafarers who lived for considerable periods of time almost exclusively on salt meat. Already in the 18th century some long-distance travellers (Anson, Cook, Lind) discovered that fresh food, fruit (especially, limes and oranges) and vegetables were the best means of fighting scurvy. A critical analysis of the various assumptions of the causes of scurvy led V. Pashutin at the end of last century to the conclusion that scurvy was caused by food deficient in some organic substance which the human organism could not synthesize.

In the countries of Asia where the population subsists almost entirely on rice the people are widely affected by beriberi, a disease which manifests itself in emaciation, cramps and paralysis of the limbs, finally leading to muscular atrophy and death.

In the nineties of last century Eijkman, a Dutch physician, ascertained that a disease resembling beriberi (polyneuritis) may be experimentally produced in birds (chickens and pigeons) by feeding them polished rice, i.e., rice deprived of its coating. Feeding them unpolished rice or rice polishings cured them of this disease. This study put on the agenda the question of isolating the active principle which prevents the disease. In 1910, the Polish scientist Funk succeeded in obtaining a preparation from rice polishings several milligrams of which cured a pigeon suffering from experimental polyneuritis. Funk named this substance *vitamin*.

It was subsequently found that such diseases as pellagra, rickets, etc., were due to food deficient in substances referred to as vitamins. The daily need of the organism in vitamins is very low and is measured by milligrams and even fractions of a milligram.

Animal and vegetable products contain very little vitamins. Tons of substance must sometimes be processed in order to isolate a fraction of a gram of vitamin. Nevertheless, food deficient in vitamins leads to serious suffering, called *avitaminosis*. A less pronounced vitamin deficiency is known as *hypovitaminosis*.

The presence or absence of any particular vitamin and its amount are determined by biological tests. The animal is kept on a diet which contains all the necessary nutritive substances and vitamins except one. When the animal develops avitaminosis the substance studied for its content of the vitamin is added. If the substance contains enough of this vitamin the symptoms of avitaminosis are relieved or completely eliminated. Now that the chemical nature of most of the vitamins is known there are chemical methods of detecting and determining the quantity of vitamins.

The chemical composition and structure of vitamins were not exactly known for a long time. The discovery of a vitamin of the amine group in one of the preparations suggested to Funk the term vitamin, i.e., "vital amine." It is now well known that some of the vitamins not only lack the amine group but are even non-nitrogenous bodies. The different vitamins are designated by letters of the Latin alphabet (A, B, C, D, E, etc.) as well as by special terms which reflect the chemical nature or the physiological action of the vitamin.

According to their physicochemical properties, in particular their solubility, vitamins are divided into two groups—fat soluble and water soluble vitamins. The first group includes vitamins A, D, E, and K, the second—vitamins of the B complex (B_1, B_2, etc.), vitamins PP, C, etc.

Fat Soluble Vitamins

Vitamin A. Because of its action vitamin A is called the ***vitamin of growth*** or the ***antixerophthalmic*** vitamin. Lack of this vitamin in the food retards the growth of young animals (Fig. 136). In addition, A-avitaminosis gives rise to *xerophthalmia*, an ailment characterized by a drying and subsequent ulceration of the cornea. In a vitamin A deficiency wounds heal very slowly. Finally, lack of vitamin A causes nyctalopia, i.e., the inability to see at night (night-blindness).

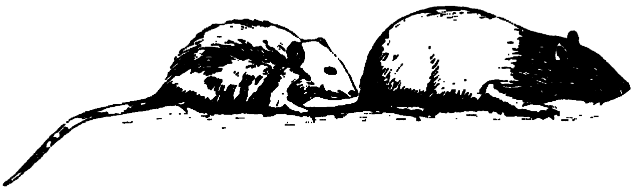

Fig. 136. Two rats of same litter: left—raised on food containing sunflower-seed oil; right—same food, but with butter containing vitamin A.

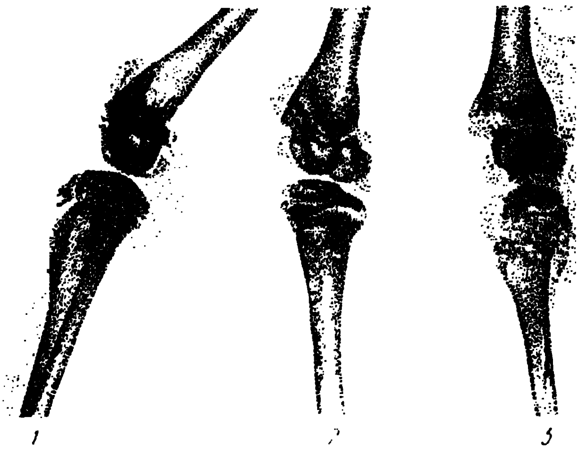

Fig. 137.

1 radiograph of bones of the normal 3-month-old rabbit; 2 the same, afflicted with rickets (2 months' avitaminosis); 3 same in severe rickets (3.5 months' avitaminosis).

In its chemical structure vitamin A is close to *carotene*, a vegetable pigment, with the formula of $C_{40}H_{56}$. By incorporating 2 particles of water beta-carotene forms two particles of vitamin A. Carotene is transformed into vitamin A in the wall of the small intestine and in the liver. Carotene is, thus, a provitamin A. Vitamin A is no longer a hydrocarbon like carotene, but a mono-atomic alcohol. In the absence of oxygen it is thermostable. In a vacuum it can even be distilled. Heated in the presence of oxygen it is oxidized and loses its biological activity. Vitamin A and carotene are found in considerable amounts in butter, egg-yolk, liver, kidneys and certain vegetables—carrots, tomatoes and spinach. Vitamin A is particularly abundant in cod-liver oil.

A considerable amount of the product of vitamin A oxidation—***retinene***—is found in the retina of the eye. Retinene is an aldehyde which corresponds to vitamin A and which in combination with protein yields *rhodopsin* or *visual purple*. Visual purple sensitizes the retina of the eye to light and takes part in adaptation. In the light the visual purple breaks up into retinene and protein (*opsin*). In the dark visual purple is resynthesized from retinene or vitamin A and opsin.

Vitamin A is used as a medicine to accelerate the healing of wounds and ulcers, especially in ophthalmological practice. The amount of vitamin A required for preventing avitaminosis in man corresponds to 1 to 3 mg. (or 3 to 5 mg. carotene).

Group of vitamins D. D-avitaminosis sharply manifests itself only in childhood in the form of *rickets*. In rickets the bones fail to calcify properly. The content of calcium and phosphorus in rachitic bones is greatly reduced. Owing to this the sutures of the skull and the fontanels do not close, the bones of the limbs become too flexible and curve under the weight of the body, the epiphyses do not ossify (Fig. 137), a rachitic rosary is formed at the osteochondral junctions of the ribs because the bones fail to ossify, etc.

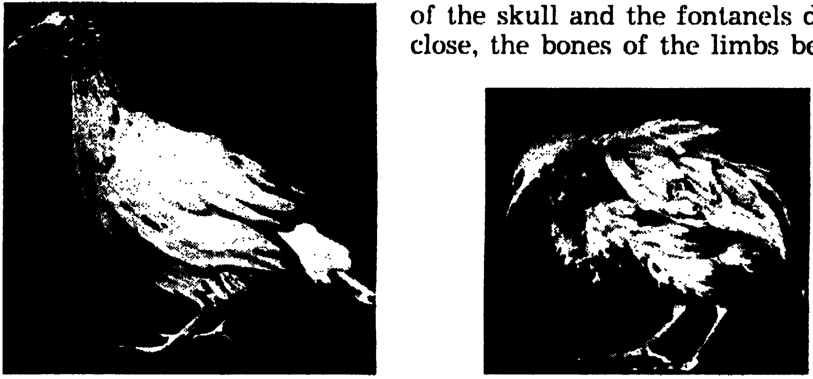

Fig. 138. Two chicks of same brood raised on food deficient in vitamin D. Left—with sufficient sunlight, right—with limited sunlight (after McCollum).

In addition to food rich in vitamin D successful treatment of rickets also requires sufficient amounts of the salts of calcium and phosphoric acid in the food and sunshine. This complex interrelationship has now been essentially ascertained.

Vitamin D may be found in a number of foodstuffs in two forms—vitamin and provitamin. The provitamin is transformed into a vitamin by solar or quartz lamp irradiation (Fig. 138). The active part of the ultraviolet rays is the long-wave part (about 300 $m\mu$). Ultraviolet rays of a shorter wavelength destroy vitamin D.

The first substance whose provitamin nature was discovered was *ergosterol*, found in large amounts in ergot and yeast. By irradiating it an active antirachitic preparation—calciferol or vitamin D$_2$—was obtained.

Subsequent studies revealed the existence of other provitamins—22, 23-dehydroergosterol, 7, 8-dehydrocholesterol and some others. The 7, 8-dehydrocholesterol is a natural provitamin which is always found in man and animals and which changes to vitamin D$_3$ under the action of ultraviolet rays. There are, thus, several vitamins D with antirachitic activity.

The egg-yolk and the liver contain considerable quantities of vitamin D. Cod-liver oil is especially rich in vitamin D. Cod-liver oil is used as a medicine in rickets. Provitamins D are found wherever there is cholesterol, particularly in the skin. This explains the importance of sunlight in the treatment of rickets. Under solar radiation the photochemical reaction causes a new substance—vitamin D—to form from the cholesterol; the body itself is incapable of synthesizing this vitamin.

In an optimum correlation between the calcium salts and phosphoric acid in the food the daily amount of vitamin D required to safeguard a child against avitaminosis is negligible and is measured by micrograms ($1 \mu g. = 0.001$ mg.). Twenty mg. is considered the daily requirement in child feeding.

Consumption of excessive amounts of vitamin D (hundreds and thousands of times the required quantities) for a long time results in *hypervitaminosis* D, which manifests itself in a higher concentration of calcium and salts of phosphoric acid in the blood, in an increased calcification of the bones and in the storing of the salts of calcium in a number of organs.

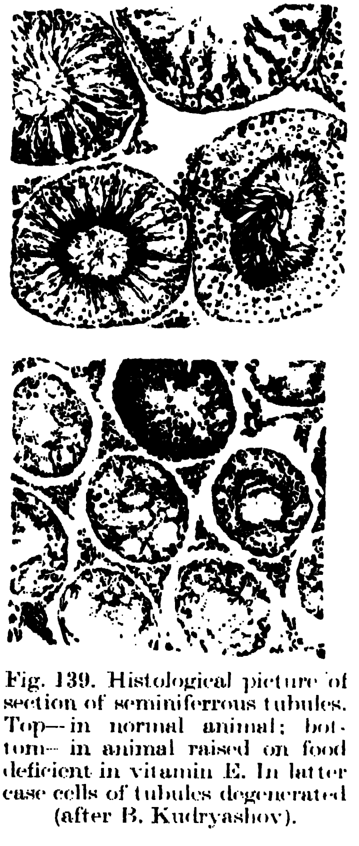

Fig. 139. Histological picture of section of seminiferrous tubules. Top—in normal animal; bottom—in animal raised on food deficient in vitamin E. In latter case cells of tubules degenerated (after B. Kudryashov).

Vitamin E. E-avitaminosis manifests itself in animals in a loss of fertility. The deficiency in this vitamin prevents pregnancy, and if pregnancy has already begun causes the destruction of the foetus, its resorption in the uterus or a miscarriage. The males suffer atrophy of the germinal cells of the testes and fail to produce spermatozoa (Fig. 139). Nursing animals develop lactation (secretion of milk) disorders. Lack of vitamin E also causes a muscle ailment (muscular dystrophy).

Vitamin E restores the normal state of the sex organs and ensures the continuation of pregnancy and normal childbirth. Vitamin E has, therefore, been named tocopherol (tocos—childbirth). There are three isomers of tocopherols (α, β and γ) differing as to their biological activity.

Vitamin E is found in the germ of many seeds, in the green parts of plants and in some animal tissues (hypophysis, placenta).

Vitamin K. Vitamins K (K_1 and K_2), derivatives of naphtoquinone, are also known as *antihaemorrhagic vitamins*. A deficiency of these vitamins in the food results in the inability of the blood to coagulate; animals with K-avitaminosis develop haemorrhagic tendencies. The reason for it is that the prothrombin fails to synthesize in the liver.

Vitamin K is very abundant in nature. It is found in foodstuffs of both animal and vegetable origin. K-hypovitaminosis usually develops in people not because of a vitamin K deficiency in the food, but because of its failure to be absorbed, which is due to the fact that bile does not reach the intestinal tract.

The naphthoquinone ring is of decisive importance in the activity of vitamin K. The change in the length of the side hydrocarbon chain is of secondary importance. It has, thus, been possible to obtain a large number of naphthoquinone derivatives which, in some measure, act like vitamin K. *Methylnaphthoquinone* (*methynone*) and *vicasol*, a bisulphite derivative of methylnaphthoquinone synthesized by A. Palladin, prove to be the most convenient for medical practice. Vicasol dissolves well in water and is, therefore, more conveniently administered parenterally than any other vitamin K preparation. Administered *per os* vicasol can be absorbed even if the bile duct is occluded.

Vitamin B Complex

The factor, whose deficiency in the food causes beriberi in man and experimental polyneuritis in animals, has been named vitamin B. Experiments on growing animals have also shown that a deficiency in this factor inhibits growth. It was subsequently found that there were several factors in the water-soluble preparations of vitamin B.

Vitamin B_1. The first vitamin of the vitamin B complex to be discovered was the one whose deficiency caused beriberi and experimental polyneuritis. It was designated as vitamin B_1, the *antineuritic* vitamin or *aneurin.* This vitamin contains an amino-group connected with a pyrimidine ring and sulphur in a thiazol ring. Hence, one more name—*thiamin.*

Vitamin B_1 is soluble in water and slowly disintegrates when heated. The following foodstuffs are rich in vitamin B_1: brewers' yeast, the germs and coatings of the seeds of certain grains (wheat and rye), kidneys and liver.

Beriberi was widespread where the people subsisted almost exclusively on rice, especially on polished rice—in Japan, China and in Malaya. The disease begins with emaciation, locomotor disorders and loss of sensitivity in the legs. The muscles of the extremities become atrophied with a resulting paralysis of the arms and legs. Experimental polyneuritis in birds, kept on a diet deprived of vitamin B_1 (polished rice), may manifest itself in several forms. Locomotor disorders, and sustained contraction of the occipital muscles with the head thrown back—opisthotonos—are observed in the spastic form (Fig. 140). The spastic form may pass into paralytic or even the atrophic form. These manifestations are due to an affection of the nervous system. Since a number of nerves are affected this ailment is called *polyneuritis.*

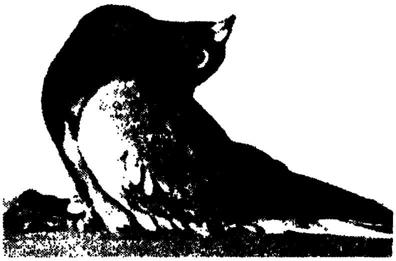

Fig. 140. Experimental polyneuritis in pigeon kept on food deficient in vitamin B_1 (cramp of posterior cervical muscles—opisthotonos).

The nervous system is affected in B_1-avitaminosis because of the deranged intermediate carbohydrate metabolism in which the brain tissue consumes less oxygen and accumulates pyruvic acid. To oxidize the latter the animal organism requires an enzyme—oxidase of pyruvic acid. Cocarboxylase, which is a pyrophosphoric ester of vitamin B_1, is a coenzyme of this oxidase. It follows that in a deficiency of vitamin B_1 the co-carboxylase cannot be synthesized in sufficient quantities owing to which the oxidase of pyruvic acid in the animal proves insufficiently active.

Man requires 2 mg. of vitamin B_1 per day. An increased consumption of carbohydrates (for example, in muscular work) requires more vitamin B_1. If a greater part of the carbohydrates is replaced with fats and proteins the requirement of vitamin B_1 drops to a fraction of a milligram.

Vitamin B_2. The growth factor B_2 belongs to the group of *flavins*, substances widespread in various tissues; they have a yellow colouring and a yellow-green fluorescence. In a deficiency of vitamin B_2 the growth of young animals is retarded. In addition, a deficiency of this vitamin sometimes causes in human beings an eye ailment (vascular keratitis), affection of the mucosa of the mouth, etc. The flavin, which is isolated from milk and known as *lactoflavin* or *riboflavin* has been studied best. Riboflavin is a compound of ribityl alcohol and a heterocyclic system called *isoalloxazine*. It is one of the yellow or flavin enzymes. These enzymes take part in oxidizing the reduced codehydrase and a number of intermediate products of metabolism (amino acids, xanthine, hypoxanthine, etc.).

Man requires 2 mg. of vitamin B_2 per day.

Vitamin B_6. Vitamin B_6 or *pyridoxine* is a derivative of pyridine. In the animal body it is oxidized to *pyridoxal*. The phosphoric ether of pyridoxal is a coenzyme of amino-pherase (enzymes taking part in reamination) and decarboxylases (enzymes which liberate CO_2 from amino acids and form amines). In a deficiency of pyridoxine in the food multiform disorders (dermatitis, anaemia, muscular cramps) variously manifest themselves in different animals.

Vitamin PP or antipellagra vitamin. A deficiency of this vitamin in the food leads to pellagra. Pellagra is most widespread where maize is nearly the only food. This disease manifests itself in erythema, blisters on the skin which leave lesions or pigmentation. The mucosa in the oral cavity, especially on the tongue, swells and is frequently ulcerated. The nervous system, both peripheral and central, is also affected.

In its chemical nature vitamin PP is a derivative of pyridine, namely, an amide of nicotinic acid. Nicotinic acid itself has the properties of vitamin PP.

The amide of nicotinic acid, like vitamins B_1 and B_2, forms part of the enzymatic systems contained in all cells. It is precisely the amide of nicotinic acid that together with adenine forms part of dinucleotide which is a coenzyme of dehydrase (*cozymase* or *codehydrase*). Codehydrase forms part of the oxidative fermentative system and serves as the carrier of hydrogen from the oxidated substratum (lactic acid, alcohol, phosphoglycerine aldehyde, etc.) to the flavin enzymes. Man requires about 15 mg. of vitamin PP per day.

Other vitamins of the B complex. *Pantothenic acid, biotin, para-aminobenzoic acid, folic acid,* and *vitamin* B_{12} belong to this group of vitamins. Of particular interest to medicine are folic acid and vitamin B_{12}. A deficiency in the former causes macrocytic anaemia, while a deficiency in the latter results in pernicious anaemia.

Pernicious anaemia had long been considered an incurable disease. In the beginning of the 20th century it was discovered that it could be successfully treated by adding half-raw liver to the diet. Extracts obtained from liver tissue were subsequently used in the treatment of anaemia. The liver contains an antianaemic factor which stimulates blood formation. It was supposed that in healthy people with a normal diet the formation of this factor involved two constituents of which one was supplied by the food (extrinsic factor), while the other (intrinsic factor) was formerly regarded as an enzyme formed in the mucosa of the stomach. Failure of the intrinsic factor to form was considered the cause of pernicious anaemia.

With the discovery of vitamin B_{12} it was ascertained that this substance should be regarded as an extrinsic factor. In entering the stomach vitamin B_{12} combines with a special protein—apoeritein, and in this combination the vitamin is protected from destruction by the digestive juices. In patients with pernicious anaemia the apoeritein is destroyed because of the low acidity of gastric juice.

Thus, the first cause of pernicious anaemia is, apparently, achlorhydria, i.e., failure of hydrochloric acid to form during the secretion of gastric juice.

Inositol and *choline* are also reckoned among vitamins. The latter, however, can be synthesized in the organism and cannot be properly regarded as a vitamin.

Vitamin C

A deficiency of vitamin C in the food, usually due to a lack of fresh vegetables and fruit in the diet, causes scurvy. Hence, the other name for vitamin C—*ascorbic acid*. Haemorrhages in the skin and in the mucous membranes are the most vivid symptom of scurvy. It is believed that this is due to the increased permeability of the blood vessels because of changes in the properties of the intercellular substance which lies between the endothelial cells of the capillaries. The mucous membranes become ulcerated and the gums swollen. There are atrophic changes in the bones, loosening of the teeth and swelling of the joints. Scurvy is particularly cruel to children (Meller-Barlow disease). They suffer haemorrhages in the bones and in the internal organs. Without adequate treatment children die fast. All the morbid phenomena disappear when foodstuffs rich in vitamin C are introduced into the diet or this vitamin in its pure form is injected.

It is impossible to cause experimental scurvy in some animals (rats, pigeons) even when they are fully deprived of vitamin C. In this case the tissues of these animals retain ascorbic acid which indicates that, unlike man, certain animals are capable of synthesizing ascorbic acid.

Ascorbic acid is very easily oxidized owing to which vitamin C is rapidly destroyed when heated in the air. An alkaline reaction aids in oxidizing vitamin C, while an acid reaction helps to preserve it.

In the animal tissues ascorbic acid is found in all cells. It is particularly abundant in the adrenals, the brain tissue and the liver. Because of its ability reversibly to be oxidized and reduced ascorbic acid can take part in oxidative processes. In addition, it activates certain intracellular enzymes (the proteolytic enzyme cathepsin, arginase and amylase). Ascorbic acid takes part in the metabolism of tyrosine.

Of the vegetable foods ascorbic acid is found in considerable quantities in spinach, cabbage, lettuce, lemons, oranges and apples. It is even more abundant in black currants and, especially, in the soft part of the fruit of briar. Man requires 50 mg. of ascorbic acid per day.

There are indications that lemon juice and fresh vegetables are a better antiscorbutic means than crystalline ascorbic acid. It is, therefore, assumed that in addition to ascorbic acid prevention of scurvy requires *citrin* (a flavone derivative extracted from lemon juice) or kindred substances.

Biological Role of Vitamins

Vitamins, as essential factors in nutrition, are required not only by man and the higher animals, but also by the lower animals and even microbes. However, some animals do not need all of the aforesaid vitamins. For example, besides man only monkeys and guinea-pigs need vitamin C. Rats do not need either vitamin C or vitamin PP in their food because these vitamins can be synthesized in their organisms. Glucose and glucuronic acid are the initial substances for the synthesis of ascorbic acid.

Upon entering the tissues of animals most of the known vitamins undergo certain biochemical changes. For example, vitamin A (axerophthol) is oxidized so that an aldehyde group replaces the alcohol group and a new body —retinene or axerophthol—is formed. Pyridoxine is similarly oxidized with pyridoxal formed as a result. A number of vitamins or their derivatives are phosphorylated (vitamins B_1 and B_2, and pyridoxal). In some cases there are further conversions (formation of codehydrase, etc.). In a number of instances the substances thus formed react with specific proteins, as a result of which certain enzymes are formed. Vitamin B_1 forms part of carboxylases and dehydrases, vitamin B_2 is a constituent of a number of flavin enzymes, vitamin PP—of a number of dehydrases, pyridoxal—of aminopherases. Pantothenic acid forms part of coenzyme A, a coenzyme of the system of acetylating enzymes, biotin is a constituent of an enzyme that takes part in binding CO_2. It is, therefore, clear why the organism needs vitamins and why it is possible to satisfy it with a very small amount of these substances.

In some cases the vitamins that have a certain chemical structure can be replaced by natural or synthetic substances with a very similar structure. It appears there is not one vitamin D, but a whole group of them; the same is true of vitamins E and K. Substances were synthesized which, slightly differing from vitamins B_1, B_2 and C in chemical structure, seem to have some measure of the biological activity of these vitamins. These substances are called *homovitamins*.

In addition to the discovery of homovitamins it has been possible to find and synthesize substances which have an opposite effect and are, therefore, called *antivitamins* or *pseudovitamins*. These substances aggravate avitaminosis causing it even when there is sufficient vitamin in the body or producing avitaminosis in an animal in which it cannot be produced by excluding the vitamin from the food. For example, by feeding rats pyridine-3-sulphonic acid (antivitamin PP) it is possible to produce in them symptoms of PP-avitaminosis.

This activity of antivitamins is explained by the competition between them and the vitamins during the interaction with the specific protein part of an enzyme. The resemblance between the structures of an antivitamin and vitamin makes possible the formation of specific protein complexes with both. However, the complex of an antivitamin with a protein does not result in the formation of an active enzyme. The deficiency in the latter is what finally leads to disorders characteristic of avitaminosis.

A similar relationship is observed in the world of microorganisms. Many pathogenic microbes need para-aminobenzoic acid as a factor of growth. The part of antivitamins, as regards this acid, is played by sulfanilamide preparations, particularly white streptocide. The addition of streptocide inhibits the growth of these microbes. Hence, the importance of sulfanilamide preparations as chemotherapeutic means, i.e., chemical means for the treatment of infectious diseases.

In highly organized animals it is the central nervous system that is particularly sensitive to vitamin defficiency. It suffers especially in B_1-, PP- and E-avitaminosis. There are also indications that a deficiency in vitamin C causes a decrease in cerebral oxygenation.

CHAPTER 33

MINERAL AND WATER METABOLISM

Biogenic Elements

The biogenic elements include the essential constituents of animal and vegetable organisms without which these organisms cannot exist. According to the studies of V. Vernadsky's school most of the elements of the periodic system form part of living organisms. It is believed, however, that some of them are constituents of the organism accidentally, due to the peculiarities in the composition of the environment. The following elements have been found in the composition of animal and vegetable organisms:

Nitrogen
Aluminium
Boron
Bromine
Vanadium
Hydrogen
Iron
Iodine
Potassium
Calcium
Oxygen
Cobalt
Silicon
Magnesium
Manganese
Copper
Molybdenum
Sodium
Nickel
Sulphur
Carbon
Phosphorus
Fluorine
Chlorine
Chromium
Zinc

The elementary composition of different animal organisms greatly varies, mainly in its water content. The body of a jellyfish contains 98 per cent water, the body of a snail—84.4 per cent and that of a guinea-pig—73.6 per cent. The solid residue of these animals varies between 2 per cent (jellyfish) and 26.4 per cent (guinea-pig). The body of a human adult contains 35 to 42 per cent solid substances.

The studies of the elementary composition of the solid substances in the bodies of animals reveal relatively close figures. In examining sea and river plankton, the bodies of a snake, mouse and guinea-pig, A. Vinogradov and V. Sadikov found the carbon content for all these representatives of the animal world to be within 43 to 49 per cent, hydrogen—7 to 7.5 per cent, nitrogen—8 to 11 per cent, and mineral ash—11 to 18 per cent. For the human body Bertrand cites the following figures:

Elements	Content in % to dry residue
Carbon	48.43
Oxygen	23.70
Nitrogen	12.85
Hydrogen	6.60
Calcium	3.45
Sulphur	1.60
Phosphorus	1.58
Sodium	0.65
Potassium	0.55
Chlorine	0.45
Magnesium	0.10

The foregoing figures should be regarded only as approximations. Since the chemical composition of various tissues and of the different structures of the same tissue differs it is impossible accurately to calculate the content of any particular element. This is why the figures cited in scientific literature for certain elements (potassium, sodium, sulphur, phosphorus, chlorine and magnesium) differ so widely. The essential fact, however, is that the total content of these elements exceeds 99.9 per cent of the weight of the dry residue. Thus, the animal body contains very little of the other elements (iron, copper, manganese, cobalt, zinc). For this reason these elements are joined in a group of so-called *microelements* from the biological point of view. The physiological role of a number of microelements, as will be shown below, is very essential.

Mineral Metabolism

Metabolism of phosphorus. The main mass of phosphorus in the human body is in the bones in the form of phosphorus-calcium compounds. Monometallic and bimetallic salts of phosphoric acid are found in all cells and intercellular fluids. Certain intermediate products of carbohydrate metabolism (phosphohexoses and phosphotrioses) are esters of phosphoric acid. Phosphoric acid forms part of the coenzymes of respiration and glycolysis. It is a constituent of some lipoids (phospholipids or phosphatides). Finally, some of the protein groups (phosphoproteins and nucleoproteids) also contain phosphoric acid.

The incorporation of phosphoric acid or phosphorylation is of considerable importance to the processes of absorption and intermediate metabolism of a number of substances. Phosphoric acid, thus, participates in the metabolism of most of the essential groups of substances—proteins, fats, carbohydrates, vitamins, etc. In addition, the salts of phosphoric acid and its esters play the part of buffers in maintaining the acid-base balance in the tissues.

Phosphorus is assimilated in the form of salts of phosphoric acid. It is eliminated from the organism partly through the mucosa of the large intestine, but mainly with the urine. Phosphates are the principal buffer substances in the urine. The amount of phosphoric acid taken in with the food constitutes (in terms of the phosphoric anhydride—P_2O_5) 2.5 gr.

Metabolism of sulphur. Sulphur enters the organism as part of the proteins. It is found in the latter in a bivalent, i.e., unoxidized, state forming part of amino acids (cystine and methionine). Some proteins—mucin and mucoids—contain sulphur in an oxidized state. The bivalent sulphur is oxidized in the organism forming a number of products, particularly taurine which later forms part of taurocholic acid. Sulphuric acid is used for rendering a number of toxic substances harmless (phenols, indoxyl and other products); these substances take their source in the products of protein conversion putrefying in the large intestine. The main part of sulphur is excreted with the urine in the form of salts of sulphuric acid, the much lesser part—in the form of twin compounds of sulphuric acid with phenols and indoxyl (indican) and, finally, a negligible part of sulphur is eliminated unoxidized as part of cystine. The daily amount of eliminated sulphuric acid constitutes (in terms of the phosphoric anhydride—SO_3) about 2.5 gr.

Metabolism of calcium and magnesium. Osseous tissue contains a very high percentage of calcium (8 per cent and even more of the total fresh bone). The mineral composition of bone is quantitatively close to the formula—$3\,[Ca_3(PO_4)_2] \cdot CaCO_3$. In addition to the constituents shown in the formula the bones contain a small amount of magnesium, potassium, sodium, chlorine and fluorine. The skeletal system is the main calcium depot.

The tissue fluids, particularly the plasma of the blood, also contain calcium. Part of it is, in this case, in an ionized state, another part is in the form of nonionized compounds in true solution, and the third part is combined with proteins. All three forms of calcium are in a state of mutual equilibrium and the reagents, which precipitate the ionized calcium, precipitate all these forms.

The plasma of the blood does not contain much calcium—10 mg. per cent. The calcium ions activate the formation of thrombin, the enzyme that coagulates blood. The constant concentration of calcium in the blood is very important in maintaining the nervous and muscular tissue in a normal state of excitability. A fall in the concentration of calcium in the blood plasma causes an accelerated heart rate and increased excitability of the nervous and muscular systems which leads to tetany (p. 422). The cells have none or very little calcium.

The daily calcium requirements depend on a number of factors; on the nature of food and on the condition of the body. Under normal conditions the body needs from 0.6 to 0.8 gr. calcium per day. During growth and pregnancy large amounts of calcium are required for bone-building.

In a calcium-deficient diet of adults the calcium requirements of the organism may be satisfied for months and even years at the expense of the skeletal system.

Calcium is absorbed from the intestines mainly in the form of complex compounds with bile acids. It is eliminated partly with the urine and partly through the mucosa of the large intestine with the faeces in the form of calcium carbonates and calcium phosphates. The amount of calcium eliminated by the second method depends on the quantity of calcium phosphates in the food: the more of them in the food, the greater the part excreted with the faeces. The nature of the food is also very important. In a vegetable diet, which causes a shift towards alkalosis in the organism, the greater part of calcium is excreted through the intestines. A meat diet, which fosters acidosis, increases the elimination of calcium with the urine. The addition to the diet of substances which cause a shift in the acid-base balance in either direction causes corresponding changes in the excretion of calcium.

The metabolism of calcium consumed by the body is influenced by a number of food factors: the content of phosphates in the food, the proportion of acids and bases formed during the metabolic processes and, finally, the content of vitamin D. In the absence of the latter, even if sufficient calcium is absorbed by the body, ossification does not proceed normally.

The concentration of calcium in the blood is regulated by the hormone of the parathyroid glands. A derangement in the function of the latter is attended by a lower concentration of calcium in the blood which causes higher excitability in the neuromuscular system manifested in cramps (tetany, p. 422).

Unlike calcium, magnesium is found mainly in the intracellular substance. The tissue fluids and the bones contain much less magnesium than calcium. In the cells magnesium forms part of certain enzymatic systems involved in glycolysis. Subcutaneous or intravenous injection of magnesium results in somnolence and even in anaesthesia. The body consumes and excretes magnesium the way it does calcium.

Metabolism of sodium and potassium. Sodium and potassium are found in the organism in the form of chlorides, bicarbonates and phosphates. A small part of them is bound by organic salts and proteins. The distribution of these two cations in the body differs. Sodium is a quantitatively prevailing cation in the blood plasma and in the tissue fluids. Three-quarters of the osmotic pressure in these fluids is determined by the sodium chloride they contain. The regulation of the sodium-ion content and its concomitant chlorine-ions is, therefore, one of the ways of maintaining a definite osmotic pressure which, in its turn, causes the passage of water in the tissues in either direction. The cells contain a negligible amount of sodium.

Potassium is, on the contrary, concentrated in the cellular masses where its content reaches 300 to 400 mg. per cent. There it is partly bound by proteins. Potassium-ions are necessary for the activation of certain enzymatic systems. The blood plasma and the intercellular fluids contain only 20 mg. per cent potassium. An increase in the content of potassium in the blood plasma to 60 mg. per cent, attained under special experimental conditions (injection of potassium salts into an animal with extirpated adrenals), quickly kills the animal. At the same time complete elimination of potassium from the fluid passed through the heart leads to cessation of cardiac contractions. Experiments in which artificial radioactive potassium was injected have shown that despite the great difference in the content of potassium there is a constant potassium exchange between the cells and the fluid that surrounds them. The cellular membranes are, thus, not impermeable to potassium. A change in the permeability of cellular membranes occurs during excitation of muscular and neural elements and these changes are believed to be connected with bio-electric phenomena.

The hormones of the adrenal cortex (corticosterone and kindred substances) take part in regulating the concentration of potassium and sodium in the blood plasma.

If the function of the adrenal cortex is impaired the content of sodium in the blood plasma of experimental animals decreases while the concentration of potassium increases; at the same time the kidneys excrete more sodium and less potassium into the urine. In connection with this the animal grows sensitive to a greater intake of potassium with the food. Contrariwise, an increase in the amount of sodium in the food brings these animals relief. In these cases the old theory of the Yuriev professor Bunge that the necessity of consuming large amounts of sodium is connected with the necessity of excreting potassium excessively consumed with food proves right. However, this theory has not justified itself in relation to healthy animals and man for whom it was advanced.

Man requires 4 to 6 gr. of sodium and 2 to 3 gr. of potassium per day. Both vegetable and animal foods are rich in potassium. Sodium must be specially added to the food in the form of common salt. In some ailments (skin tuberculosis, kidney disorders) limited consumption of sodium chloride produces a wholesome effect. An excess of sodium chloride in children (especially if its solutions are injected subcutaneously or intravenously) causes a so-called *salt fever*.

Metabolism of chlorine. Chlorine is found in the organism exclusively in the form of chlorides, mainly in combination with sodium and to a lesser extent with potassium. Like sodium chlorine is found primarily in the intercellular fluids. The metabolism of chlorine was, therefore, frequently identified with that of sodium and was referred to as the metabolism of sodium chloride. However, chlorine forms part of certain cells, for example erythrocytes, independently of sodium. It has now been established that the metabolism of chlorine does not always run parallel with that of sodium, though it does occur in certain cases.

The usually consumed daily amount of chlorine constitutes 6 to 9 gr. The reserves of chlorides in the organism are hardly affected by decreased consumption of chlorine salts because of a corresponding decrease in the excretion of chlorides with the urine. The organism loses a lot of chlorides only by excessive perspiration, by using certain diuretics and by repeated pumping out of gastric juice if the food consumed is poor in chlorides. The loss of large amounts of chlorine by the body (about 20 per cent of the total amount) impedes the secretion of hydrochloric acid by the gastric glands.

Practically, losses of large amounts of chlorides by the human organism are encountered during sustained physical work under conditions favouring overheating. Marching, hard physical work in a hot climate and work in hot shops or in deep mines increase the amount of sodium chloride lost with the perspiration which may reach 20 gr. and even more. Its excretion with the urine decreases until chlorine-ions fully disappear from the urine. But when such large quantities of chlorides are lost the losses cannot be fully compensated by decreased excretion of chlorides with the urine. The body grows poor in sodium chloride which is manifested in a grave condition attended by cramps. Consumption of additional quantities of common salt prevents this condition.

Microelements and Their Role

Iron is found in the body in the form of organic and inorganic compounds, which include haemoglobin, myoglobin, etc.

Iron is absorbed in the form of inorganic compounds. Entering the intestinal wall, the spleen and the liver it is stored in the form of *ferritin* which is a compound of a hydrate of ferric oxide and protein. Ferritin can be utilized for synthesizing organic iron-containing compounds. During decomposition of haemoglobin and other haem-containing compounds iron combines either with the *haemosiderin* pigment or with ferritin again.

Iron is excreted by the mucosa of the large intestine. This circumstance had long impeded the solution of the problem as to the compounds and amounts in which iron was assimilated. It has been found that it is absorbed in the upper portion of the intestine in the form of iron oxide and excreted in the lower portion of the intestine in the form of ferric oxide.

Man needs 13 to 15 mg. of iron per day. The growing organism requires more—about 0.5 mg. per one kilogram of bodyweight. Meantime, milk, which is the baby's only food, contains very little iron. The needs of the infant are covered by the reserves of iron in the liver stored in the body before birth. The iron requirement during pregnancy is, therefore, higher.

Copper is an element also necessary to life. Porphyrin compounds containing copper and resembling the haem (turacin in bird feathers) are known. In some lower animals copper forms part of the blood pigment (haemocyanin). The higher animals need copper to stimulate the formation of erythrocytes in which a copper-containing protein (haemocuprein) has been found. Copper forms part of some oxidative vegetable enzymes.

Manganese, apparently, forms part of certain oxidative enzymes; it activates arginase and some proteolytic enzymes.

The organism requires several milligrams of **zinc** per day. The latter forms part of carbon anhydrase (an enzyme) and is a constant admixture in insulin preparations. There are indications that zinc has something to do with cell reproduction. It is found in greater quantities in tissues capable of vigorous reproduction or containing many nucleoproteids (liver, sexual glands, tissues of malignant tumours).

Cobalt forms part of vitamin B_{12} necessary for normal blood formation. Lack of cobalt in the soil of pastures leads to epizootics.

In some of the lower animals **silicon** is the main constituent of the external skeleton. The connective tissues of the higher animals always contain a certain amount of silicon. People working in an atmosphere of silicate dust develop so-called *silicosis* of the lungs because the silicate dust penetrates into the lung tissues.

Bromine in its metabolism parallels chlorine. The blood and the tissues contain small quantities of it. Taken in certain amounts bromides intensify the processes of inhibition in the cerebral cortex and re-establish the equilibrium between the processes of excitation and inhibition. When large quantities of bromides are consumed HBr is secreted in the gastric juice together with the HCl.

Iodine forms part of thyroxin, the hormone produced by the thyroid gland. Its total content in the organism is negligible—about 0.025 gr. Nevertheless, a deficiency in iodine in the food and drink results in serious ailments—endemic goitre, myxoedema and cretinism (see chapter on the thyroid gland).

Fluorine forms part of the dental enamel. In a deficiency of fluorine in drinking water human teeth easily decay (caries).

Chromium. There are indications that chromium salts take part in activating trypsin.

The role of a number of other microelements still needs investigating.

Water Metabolism

Water constitutes the greater part of the bodyweight of animals. The body of man contains approximately 65 per cent water. Its content in the different tissues varies very greatly: the skeleton contains about 20 per cent water, the liver, muscles, brain, skin, heart and connective tissue—70 to 80 per cent, the blood—about 80 per cent, and the other fluids of the body and secretions (milk, perspiration, gastric juice) 90 to 99 per cent. In the young the tissues contain more water.

Both the cells and the intercellular substances form a complex heterogeneous system the separate phases of which contain water as a necessary constituent. Aqueous solutions of mineral and organic substances fill the tiniest nuclei of cellular structures and form the basis of tissue fluids. Particles of water form part of the denser structures of which the cellular and intercellular structures are made. It is uncommonly hard, for example, to extract the last particles of water from protein preparations.

Thus, in addition to *free water* we must take into account the *bound* water in the form of *hydration water.*

Water is a fine solvent for a large number of substances and a medium in which most of the chemical reactions connected with metabolism, and consequently with life, take place.

From the physicochemical point of view water is a liquid which has a number of properties conditioned by the sharply pronounced polarity of its particles. This explains why despite its low molecular weight water is a liquid at ordinary temperatures and a solid at 0°. Substances composed of nonpolar molecules even with a higher molecular weight are gases at room temperature (carbon dioxide, hydrocarbons with up to six atoms, nitric oxide, etc.). The polar structure of the water molecules explains the extremely high dielectric water constant which aids in the electrolytic dissociation of a number of substances dissolved in water. Water itself is a weak electrolyte which dissociates into H+ and OH− ions. These ions possess the properties of catalysts which accelerate the course of a tremendous number of most diverse reactions. The polar structure of water determines the firmness of its intermolecular bonds as a result of which water has a high thermal capacity and a very high specific heat which is of great importance to the physiology of heat regulation.

The organisms of land animals take in water with drink and food. A certain amount of water is produced in the organism itself during oxidation of a number of substances. In complete oxidation 100 gr. of fat form 107 gr. of water, 100 gr. of starch—55 gr. of water, and 100 gr. of protein—41 gr. of water.

The total daily water requirement of man constitutes approximately 2.5 litres.

Water leaves the human organism through the kidneys with the urine (about 1.5 lit.), through the lungs in a vaporous state (about 400 ml.), through the intestines with the faeces (about 200 ml.) and through the skin (about 500 ml.). Water is lost through the skin by perspiration and by elimination in a gaseous state (*perspiratio insensibilis*[*]—imperceptible sweating). The latter is, apparently, a purely physical process of water permeation through the membranes and its evaporation without the participation of the sweat glands.

The aforementioned quantitative correlations may greatly alter under different conditions of existence. Thus, in some ailments (diabetes mellitus and diabetes insipidus) the kidneys may eliminate enormous quantities of water (8 to 10 litres per day). In dyspnoea during muscular work or in the mountains the amount of water eliminated through the lungs increases. During work in hot shops or in hot weather the amount of water lost through the skin may reach 6 to 10 litres. In diarrhoeas considerable quantities of water are lost through the intestines. In all these cases man experiences thirst which impels him to drink more water.

The absorbed water is carried with the blood throughout the body and is retained by various organs. The muscles and the skin are of essential importance as water depots in the organism. Experimental hepatectomy in an animal causes the latter to lose its ability to retain reserves of water in the body (V. Savich, M. Petrova et al.).

During considerable losses of water the content of the latter in the blood diminishes but slightly because the loss of water is compensated by passage of water from the tissues into the blood. The organism endures water hunger with great difficulty. By taking water the "marathon fasters" got along without food for close to 50 days. Animals can live but a few days if they consume dry food without water.

Water is eliminated by the kidneys, the skin and the intestines in the form of a solution containing salts. Retention of water by the tissues is also influenced by the content of salts in the blood and in the tissues. Salts are the principal constituents by means of which the osmotic pressure observed in the cells and in the tissue fluids is formed (p. 49). Water metabolism is, thus, closely connected with that of minerals, particularly with the metabolism of sodium chloride. We therefore often speak of water-salt metabolism. Water is best retained by the organism when taken in in the form of a salt solution isotonic to the blood. Colloid-osmotic pressure also exerts considerable influence on the redistribution of water between the blood and the tissues (p. 75).

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[*] The idea of ***perspiratio insensibilis*** includes the total loss of water through the lungs and skin without the participation of the sweat glands.

Water metabolism is, apparently, influenced by the hormones of many glands of internal secretion (thyroid, sex glands, adrenals, pancreas, liver), but the hypophysis is an especially important organ in regulating water metabolism (p. 430). The functions of the hypophysis and the other endocrine glands are in turn controlled by the central nervous system. The regulation of water metabolism is, thus, effected by the nervous system through the glands of internal secretion and the excretory systems (kidneys, sweat glands, intestines), respiration and, finally, through influencing the functional states of various tissues.

PART VIII

ENERGY EXCHANGE

CHAPTER 34

ENERGY EXCHANGE IN THE ORGANISM

In order to exist an organism must continuously exchange substances with the external environment.

All metabolic processes in the organism are attended by transformations of chemical energy into other forms of energy—thermal, mechanical, radiant and electric.

The general trend in metabolism and the exchange of energy inseparably connected with it are characterized by processes of oxidation and reduction. This is accompanied by conversion of substances rich in energy into substances with a lesser energy potential and a liberation of some form of energy.

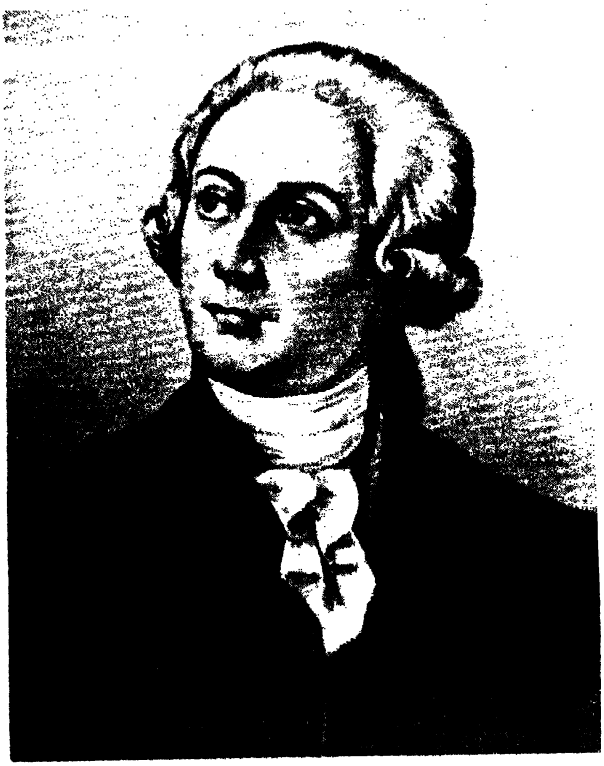
Development of Principal Ideas of Energy Exchange

The development of our knowledge of the transformations of substances in the organism is closely connected with the establishment of the principal laws of physics and chemistry, the laws of conservation of matter and energy. The first scientific postulates on these problems were formulated by M. Lomonosov who discovered the universal law of conservation of matter and motion (formulated in a letter to Eiler in 1748 and published in 1760). "All changes which occur in Nature," wrote M. Lomonosov, "are of such a character that any amount of whatever one body loses is added to another. Thus, if some matter is lost in one place it increases in another place.... This universal natural law also extends to the very rules of motion because a body that moves another body by its own force loses as much of it itself as it imparts to the body which receives its motion from it."

Lomonosov found that when iron was tempered it grew heavier because of the addition of a constituent of air. Then came the discovery of oxygen made in 1774 almost simultaneously by Scheele in Sweden, Priestley in England and Lavoisier in France. In connection with the discovery of oxygen Lavoisier showed that when coal burned or an animal breathed in a closed space its content of oxygen diminished and the content of the "gas which dulls lime," i.e., carbon dioxide, increased.

Later Lavoisier and Laplace jointly conducted their first experiments in the calorimeter they had devised. These experiments established that the amounts of heat produced by the breathing of the guinea-pig and the burning of coal were approximately equal if the same amount of carbon dioxide was liberated as a result of the burning and breathing. It consequently dawned on Lavoisier that carbonaceous substances burned in the body and he formulated his thesis: breathing is slow burning.

The relationship between the formation of carbon dioxide and the amount of heat produced, established by Lavoisier, served as the point of departure for many investigations which proved that these theses applied to man and animals alike and, thus, showed that the laws of physics and chemistry were applicable to energy transformations in the body.



Antoine Laurent Lavoisier

Subsequent studies of the problem were made by Regnault and Reiset (1849) who found there was a definite relationship between the production of carbon dioxide and the consumption of oxygen in the respiration of animals. They, too, developed the principal methods of studying gaseous exchange.

The investigations of the Dorpat physiologists Bidder and Schmidt proved very important to the development of the study of metabolism. These investigators found (1852) a considerable constancy in the production of carbon dioxide by man and animals which they observed during their studies day after day and, thus, substantiated the existence of basal metabolism (p. 354).

The construction, first by V. Pashutin (1883) and later by his pupil A. Likhachov, of a calorimeter for man and large animals represented a major achievement. The investigations conducted by Pashutin and Likhachov showed there was a strict interdependence between the amount of oxygen consumed by the body, the production of carbon dioxide and the formation of heat liberated by the organism. Thus, they established a regularity which makes it possible to use the measurements of the liberated heat or the determination of gaseous exchange for the quantitative evaluation of chemical changes in the body. Likhachov's studies, reported by him at the International Medical Congress in Rome in 1893, for the first time proved the existence of these relations between gaseous exchange and heat production, and established the applicability of the principal physical and chemical laws to the study of metabolism and energy exchange in man.

These investigations proved very important to the development of the materialist principles of biology and to the struggle against vitalism.

I. Sechenov's studies, first of the gases in the blood (Chapter 20), and later (together with his pupil M. Shaternikov) of gaseous exchange in man and animals were very important to the knowledge of metabolism.

The ideas of metabolism in the body, formed over more than 150 years, sprang from the concept that the level metabolism was strictly constant. According to these ideas metabolism changes only in connection with the work done by the body, with the intake of food, with the processes of juice secretion and absorption connected with food consumption, and with the influences exerted on the body by the temperature of the external environment. Summed up these influences determine, according to the analytical physiology of the 19th century, the general level of metabolism in the body and the energy output at each given moment of its vital activity.

These ideas were unable to explain a number of changes taking place in the body in the process of its adjustment to environmental conditions (for example, temperature), conditions of altered nutrition (for example, complete or partial starvation), repeated muscular activity (for example, training). Embracing only the narrow factual aspect of the metabolic changes the pre-Pavlovian investigators were unable to establish a relationship between the laws regulating metabolism and those governing the development of the body, i.e., the principles of evolutionary theory.

Only by studying metabolism in an integral organism in its various relationships with its environment from the positions of Pavlovian physiology has it been possible to link the studies in the energetics of the organism with the investigations of the forms and nature of the influence of labour, nutrition, sports, climate, ecological factors, etc., on metabolism (and other physiological functions). It has been shown that it is possible to develop conditioned reflexes in response to metabolism in its different manifestations (gaseous exchange, carbohydrate metabolism, protein metabolism, etc.). This has established the cardinal fact that the total vital activity of the body, reflected in the intensity of metabolism, depends on any agent in the external and internal environment of the organism, i.e., agents which are connected in time with the effect of factors that alter metabolism as inborn reflexes (for example, work, changes in temperature), owing to which they become signals for the effect of these factors.

The studies in the metabolism of man and animals conducted in this direction have shown that the "higher equilibrium" (I. Pavlov's expression) of the body with its environment is attended and determined by profound changes in all the chemical processes in the organism. This fact closely connects Pavlov's teachings with the principles of Michurin's biology. Both these teachings regard metabolism as the principal line of the organism's communication with the external environment and, hence, as one of the most important factors in the evolution of the organic world.

Studying the Energy Output in the Body

The total energy output in the body can be most accurately determined by the amount of liberated heat expressed in calories (1 large calory or 1,000 small calories correspond to 427 kg-m. of mechanical work).

The transformations of energy in the body are very complex and are not always attended by an immediate transformation of all the liberated energy into heat. In muscular contractions 20 to 25 per cent of the liberated energy is transformed into mechanical work, while a negligible part of it manifests itself in the form of electric energy. In the long run, however, all work done in the organism, all forms of energy change to thermal energy. Thus, for example, the mechanical work of the heart muscle changes to the kinetic energy of the blood stream; this kinetic energy is spent in the form of heat in the friction of the blood against the walls of the blood vessels and in overcoming the internal friction (viscosity) of the blood. The energy of muscular work is also fully transformed into heat except the work connected with lifting loads (without the subsequent lowering) to a certain height. In the latter case the kinetic energy of the muscular movement is transformed into the potential energy of the load lifted to the given height; this energy is fully changed to heat when the given load falls to the level from which it was lifted.

Part of the energy liberated in the organism is utilized for endothermic reactions of synthesizing more complex substances from simpler ones (for example, glycogen from lactic acid). This energy is not lost, but is retained in the body in the form of an increased reserve of chemical energy. In determining the total value of the energy output we do not, therefore, have to take into account the part of energy spent on endothermic reactions.

The amount of heat liberated by the body is an accurate measure of its total energy output. The measuring of the quantity of heat liberated during a reaction is called calorimetry. In order directly to measure the heat liberated by the body (*direct calorimetry*) the animal is placed in a calorimeter. The calorimeter is a hermetically sealed chamber with double walls and water circulating between the walls. The outer wall of the chamber is well insulated to prevent the loss of heat. The heat liberated by the man or animal in the chamber is transmitted to the water circulating between the walls of the calorimeter. Since the amount of water and the rise in its temperature are known it is possible to measure the total quantity of the heat liberated.

It has already been mentioned that the first calorimeter for man was built by A. Likhachov in V. Pashutin's laboratory. In this device man could only sit or lie. A larger calorimeter was built by the American investigators Atwater and Benedict. The results of their investigations confirmed the principal inferences made by A. Likhachov.

Modern calorimeters are very intricate and cumbrous, and a number of precautions must be taken to prevent the loss of heat by the device itself. However, calorimeters have made it possible to measure accurately the amount of heat liberated by the body and, thus, offered the opportunity for comparing the value of the total energy liberated by the organism in the form of heat with the quantity of oxygen consumed and carbon dioxide produced, i.e., with the value of the gaseous exchange, as well as with the caloric value of the food taken.

Table 14 shows some of these computations.

The considerable coincidence in the results obtained in studying the energy exchange by the method of direct calorimetry and the method of gaseous exchange (see p. 348) has almost made it possible to relinquish the calorimeter as an intricate and expensive device for determining the energy output; studies in gaseous exchange, i.e., *indirect calorimetry*, are widely conducted today. The studies of the caloric value of foodstuffs were of great importance to the development of the principles of indirect calorimetry.

Table 14

Energy Intake and Output (Studied with Aid of Calorimeter) in Man in 24 Hours

Energy Intake		Energy Output	
Food consumed (in gr.)	large calories	Channels of heat production	large calories
Protein 56.8	237	Heat liberated from the surface of the body	1,374
Fat 137	1,307	Heat loss with expired air	43
Carbohydrates 79.9	335	Heat eliminated with urine and faeces	23
		Heat loss with evaporation of water through the lungs	181
		Heat lost by evaporation of water from the skin	227
		Corrections	11
Total ...	1,879	Total ...	1,859*

In 1873, the Russian physiologist V. Danilevsky determined by methods of thermochemistry the different amounts of heat produced during the combustion of foodstuffs. These studies were subsequently elaborated by the German physiologist Rubner and the American physiologist Benedict.

One of the inferences of the law of conservation of energy established by the Petersburg Academician Hess states that the total energy of any chemical reaction does not depend on the course this reaction takes. If, for example, one gr. of sugar is fully oxidized to carbon dioxide and water the amount of energy liberated is absolutely the same whether the sugar was burned or oxidized by enzymes. Thus, by determining the heat produced in the combustion of foodstuffs outside the body it is possible to establish the amount of heat liberated in the body during the oxidation of the same quantity of foodstuffs.

Given the weight of the foodstuffs oxidized by the body (at a constant body weight) and the caloric value of each gram of the assimilated substance we can approximately calculate the energy output in man and animals.

The calorific capacity of foodstuffs is studied in a small calorimeter known as Berthelot's *bomb calorimeter*. The bomb calorimeter is a hermetically sealed reservoir filled with oxygen and immersed in a water bath. An accurately weighed amount of a foodstuff is placed in the reservoir; by passing an electric spark through the bomb this foodstuff is burned and the amount of heat produced by the burning of the given substance to carbon dioxide and water is recorded (in large calories) by the change in the temperature of the water in the bath. If, for example, the temperature of 4,000 gr. of water rose after burning one gr. of starch from 15 to 16.025° C it means that one gr. of starch produced $4{,}000 \times (16.025 - 15) = 4{,}000 \times 1.025 = 4{,}100$ cal., or 4.1 large calories.

Fats and carbohydrates are oxidized to carbon dioxide and water both in the bomb calorimeter and in the body. It is somewhat different with proteins because urea is one of the products of protein oxidation. During its subsequent oxidation to nitrogen, carbon dioxide and water urea liberates a certain amount of heat. To determine the quantity of heat liberated in the body during the oxidation of one gr. of protein the following simple calculation is, therefore, made: the heat produced by the combustion of the amount of urea which is formed during the oxidation of one gr. of protein in the body is subtracted from the heat liberated by the combustion of one gr. of protein in the bomb calorimeter (5.4). Since the heat produced by the combustion of the urea formed in the body from one gr. of protein equals 1.3 large calories in determining the physiological calorific capacity of proteins this value is subtracted from the heat produced by the complete combustion of the protein in the bomb calorimeter.

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* The small difference of 20 large calories is due to certain inaccuracies in the very complicated methods of calorimetry.

The calorific capacity of the nutritive substances differs in various foodstuffs, for example, for butter and beef fat, vegetable and animal proteins, etc. With the knowledge of the calorific capacity of different foods we can make the necessary estimates with considerable accuracy. Table 15 shows the calorific capacity of some foodstuffs.

Table 15

Heat Produced by Combustion of One Gram of Foods

Substance	Heat in Large Calories
Glucose	3.75
Saccharose	4.0
Starch	4.1
Pork fat	9.5
Mutton fat	9.5
Butter	9.2
Casein	5.7
Egg white	5.7
Muscles	5.7
Ethyl alcohol	7.7

Of the foods consumed the body assimilates an average of 98 per cent of the carbohydrates, 92 per cent of the proteins and 95 per cent of the fats. The production of heat resulting from the oxidation of foods is taken at 4 large calories per one gr. of carbohydrates and proteins each and 9 large calories per one gr. of fats. If we know the amount of proteins, carbohydrates and fats (in grams) consumed with the food during a certain period of time we can estimate the amount of energy spent during the same time. To do this we must multiply the amount of consumed proteins and carbohydrates (in gr.) by 4 and the amount of fats by 9, and add the products.

This method of estimating the total value of the body's energy output is called the method of food rations; it requires no instruments: the quantity of the consumed food is calculated and the caloric value of the food is computed from tables of caloric values.

This method is not accurate, however, because the body may store up some of the nutritive substances taken in with the food (mainly in the form of fat) or, on the contrary, utilize some of the substances formerly accumulated in the organism over and above those consumed with the food. Another shortcoming of this method is the impossibility of studying by it the energy output over short periods of time and the difficulty of calculating the food ration. One of its indubitable merits is that it does not interfere with the daily routine of the people under observation and that the observation is conducted under conditions closest to reality. The method of food rations is, therefore, used for controlling the general caloric value (see p. 357) of the food rations of man. The results are the more accurate the greater the number of people concerned and the longer the period of investigation. In controlling the constancy of body weight this method may serve for the summary determination of the energy expenditures of individual groups of the population, separate occupations, in closed institutions with regulated diets, etc.

Studying Gaseous Exchange as a Method of Determining Energy Output

Since there are precise relationships between the amount of heat liberated by the body, the carbon dioxide produced and the oxygen consumed it is possible to utilize the data of the studies of the gaseous exchange to determine the energy output in calories. This method is very extensively used because it is simple, the instruments are portable and results are quickly obtained.

In investigating general metabolism in addition to studying the total value of the energy expenditures it is also important to find out what substances are oxidized in the body during a certain period of time. Proteins, fats and carbohydrates are oxidized in the body in varying quantitative proportions. In order to estimate the part of proteins in the total metabolism it is necessary to determine the amount of nitrogen eliminated with the urine. Since proteins contain 16 per cent nitrogen

$$\frac{a}{x} = \frac{16}{100}; \quad x = \frac{100\,a}{16} = 6.25\,a,$$

where a is the amount of nitrogen (in grams) eliminated with the urine, and x is the unknown quantity of protein metabolized in the organism. By multiplying this value by 4.1 (physiological caloric equivalent of protein) it is easy to find the amount of energy produced in the organism by the conversion, particularly, the oxidation of protein. For practical purposes, however, it is often quite unnecessary to determine the nitrogen in the urine for estimating the total energy exchange.

The studies of heat produced by the combustion of each type of food in the bomb calorimeter show that a definite amount of oxygen consumed and carbon dioxide produced corresponds to a definite number of calories of liberated heat. Since we know the composition of the substance studied we can easily calculate the amount of oxygen it requires for its complete oxidation to carbon dioxide and water. Thus, for example, one gram-molecule of glucose weighs 180 grams and requires for its oxidation 6 gram-molecules of oxygen which take up a volume of $6 \times 22.4 = 134.4$ lit. (at 0^0 C and 760 mm. pressure). Since 3.75 large calories are liberated during the oxidation of one gr. of glucose it follows that the consumption of 134.4 lit. of oxygen which oxidizes 180 gr. of glucose leads to the liberation of $180 \times 3.75 = 675$ large calories. This means that for one litre of oxygen consumed $675 : 134.4$, i.e., about 5 large calories are liberated. In this manner the *caloric value of oxygen* is determined for each fully oxidized substance, i.e., the amount of heat liberated during the complete oxidation of the given substance to carbon dioxide and water for each litre of oxygen consumed. This value will correspond to 5.0 for carbohydrates, 4.7 for fats and about 4.85 large calories for proteins.

With knowledge of the caloric value of oxygen it is possible accurately to estimate the energy output by determining the amount of oxygen which the organism has consumed during the given period of time. Thus, by determining the gaseous exchange we can find the exact value for the energy output.

It is always possible to determine with utmost accuracy by the chemical formula (or by the weight composition of C, H and O) of a substance how many grams or fractions of a gram of this substance one litre of oxygen will oxidize.

The amount of oxygen required to oxidize a given substance, as well as the proportions of the oxygen and carbon dioxide produced during the oxidation, will depend on the chemical composition of the oxidized substance, i.e., on the proportions of the carbon, hydrogen and oxygen in it.

During the oxidation of glucose the consumption of 6 gram-molecules of oxygen is accompanied by the liberation of 6 gram-molecules of carbon dioxide:

$$C_6H_{12}O_6 + 6\,O_2 = 6\,CO_2 + 6\,H_2O.$$

Since the volume of the gram-molecules of any gas at equal temperature and equal pressure is the same it follows that during the oxidation of carbohydrates the volume of the oxygen consumed and the carbon dioxide produced will also be the same.

The ratio between the volume of carbon dioxide produced by the organism and the volume of oxygen consumed during the same period of time is known as the *respiratory quotient*. Hence, during the oxidation of carbohydrates the respiratory quotient will equal one. The ratio will somewhat differ in the oxidation of fats. The following is the formula for tripalmitin oxidation:

$$\underset{\text{Tripalmitin}}{2\,C_{51}H_{98}O_6} + 145\,O_2 = 102\,CO_2 + 98\,H_2O.$$

Since the molecule of tripalmitin contains relatively little oxygen the oxidation of tripalmitin will require very much outside oxygen. In this case the respiratory quotient will be 0.703. For other fats it is 0.70 to 0.72. In the oxidation of proteins the respiratory quotient equals approximately 0.85.

The respiratory quotient quite accurately indicates the nature of the substances oxidized in the body. If the respiratory quotient equals one or approximates this value it means that carbohydrates, or mainly carbohydrates, are being oxidized in the body; it follows that for every litre of oxygen consumed about 5 large calories will be produced. If the respiratory quotient approaches 0.7 it is mainly fats that are being oxidized in the body and about 4.7 large calories are produced for every litre of oxygen consumed.

Usually proteins, fats and carbohydrates are oxidized in the body in various proportions and the respiratory quotient is, therefore, between 0.7 and 1.

For an accurate estimate of the amount of oxidized foodstuffs and their ratios we determine the so-called nonprotein respiratory quotient; for this purpose the amount of converted protein is estimated by titrating the amount of nitrogen in the urine during a certain period of time (at least 24 hours). Then by subtracting from the total amount of oxygen consumed and carbon dioxide produced the amount of gas corresponding to the oxidation of the converted protein we get from the remaining quantities of oxygen and carbon dioxide the respiratory quotient reflecting the ratios of the oxidized fats and carbohydrates. The closer the respiratory quotient is to one the greater the part of carbohydrates in the metabolism. To simplify these computations a table has been composed also showing the part played by fats and carbohydrates in the total metabolism (Table 16).

Table 16

Part Played by Fats and Carbohydrates and Caloric Value of One Litre of Oxygen at Different Respiratory Quotients

Respiratory Quotient	Liberated by oxidation from total amount of energy		Caloric value of 1 lit. of oxygen (large cal.)
	Fats (in %)	Carbohydrates (in %)	
0.71	100	0	4.69
0.75	85	15	4.74
0.80	68	32	4.80
0.90	34	66	4.92
0.95	17	83	4.98
1.00	0	100	5.02

Table 16 shows that each respiratory quotient between 0.7 and 1 corresponds to a definite ratio between the amount of fats and carbohydrates consumed during the investigation and to a definite caloric value of oxygen (between 4.69 and 5.02). By multiplying the caloric value thus found by the number of litres of oxygen consumed during the investigation we find the amount of energy (in large calories) liberated in the organism during the same period.

The respiratory quotient accurately reflects the part played by fats and carbohydrates in metabolism only if all of the carbon dioxide formed during the given period is eliminated by the lungs and if there is no conversion of some nutritive substances into others (for example, carbohydrates into fats).

If the ventilation of the lungs increases out of proportion to the increase in the production of CO_2 in the organism (hyperventilation) the partial pressure of carbon dioxide in the alveolar air drops. The difference between the partial pressure of CO_2 in the alveolar air and its tension in the blood increases; as a result CO_2 is liberated into the lungs; this is not only the carbon dioxide produced by the metabolism in the tissues, but also the CO_2 that split off from the bicarbonates of the blood. With such "washing" of CO_2 out of the organism its amount produced during a definite period

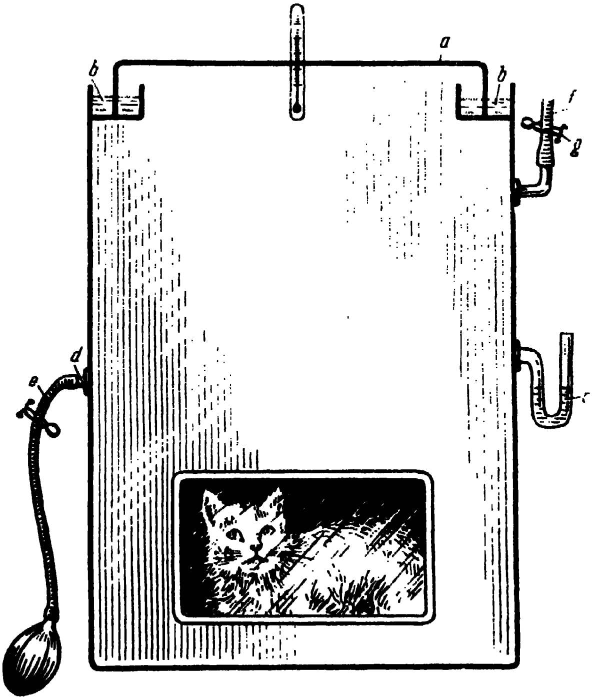

Fig. 141. Diagram of respiration apparatus.

a—lid; *b*—water lock; *c*—manometer; *d*—metal tube leading into chamber is connected with rubber hose *(e)* having clamp and bulb; *f*—rubber hose of receiver for taking samples of air. Air filling chamber is mixed by pressing on rubber bulb. At end of experiment clamp *(g)* is removed and air filling the chamber is transferred to apparatus for analysing O_2 and CO_2 content. Animal is observed during entire experiment through hermetically sealed glass.

of time does not correspond to the intensity of the oxidative changes in the body. Under the circumstances the respiratory quotient rises to 1.5 and higher. The same thing occurs when the CO_2 is displaced from the bicarbonates by acids (for example lactic acid) formed as a result of metabolism. In these cases the amount of carbon dioxide eliminated from the organism exceeds the amount of the gas produced in the processes of oxidation. The respiratory quotient rises, therefore, both in hyperventilation and in the displacement of CO_2 from the bicarbonates by the acid products of metabolism reaching 1.5 and even 2, but these values are, of course, of no significance in establishing the nature of oxidative changes in the body. When the factors causing the excess elimination of carbon dioxide from the body cease to operate the superfluous alkaline equivalents begin to bind the carbon dioxide produced in the course of metabolic changes. That is why after the rise of the respiratory quotient resulting from the "washing out" or displacement of the carbon dioxide from the blood less of this gas enters the exhaled air than is formed during the oxidative processes. The respiratory quotient then drops (to 0.4 and even lower), but this in no way reflects the chemical nature of the substances oxidized in the body. Hence, the conclusion important in determining the gaseous exchange: studies for short periods of time may be conducted only when there is a full dynamic equilibrium between the composition of the alveolar air and the gases in the blood. Otherwise it is necessary to prolong the experiment to the point when all the changes connected with the excess "washing out" of carbon dioxide (or its displacement) from the bicarbonates of the blood and its subsequent intensified binding have been equalized.

The respiratory quotient cannot be used for determining the nature of the substances oxidized in the organism when carbohydrates are intensively converted into fats, which is the case, for example, in steatosis. Since carbohydrates contain more oxygen than do fats part of the oxygen is used for the oxidative changes during the conversion of carbohydrates into fats, owing to which the amount of oxygen consumed from the air diminishes and the respiratory quotient rises. Thus, for example, the respiratory quotient in geese being fattened may reach 2. The respiratory

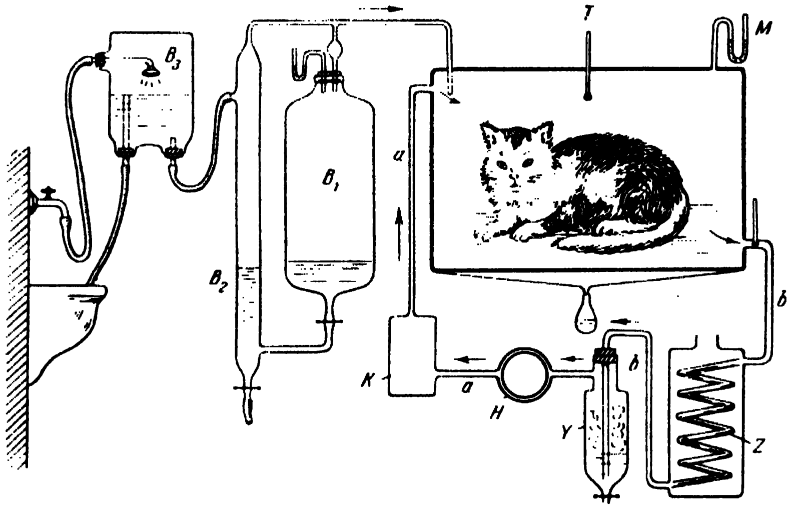

Fig. 142. Diagram of Shaternikov's closed respiration apparatus.

Motor *H* is continuously driving air through chamber along tubes *a* and *b*, through system including absorber of water vapours *(K)*, absorber of carbon dioxide *(Y)* and coil *(Z)* set in water which serves to cool the air heated by the animal. Chamber is connected with system B_1-B_3 through which oxygen is added to chamber to replace oxygen consumed by animal. Oxygen is fed into chamber automatically; amount of oxygen added is accurately measured by level of the liquid in tube B_2. In calculating gas metabolism readings of manometer *(M)* and thermometer *(T)*, installed in the chamber, are taken into consideration. Arrows show direction of movement of air and oxygen.

quotient, as has been shown above, is close to 0.7 with a fat diet and approaches 1 with a carbohydrate diet. A low respiratory quotient is usually observed in starvation because of the oxidation of fats and sometimes for the same reason when studied on an empty stomach. The determination of the respiratory quotient is the more reliable the longer the period during which the gaseous exchange is studied.

The method of studying gaseous exchange essentially consists in the fact that the composition of the inhaled (external) and exhaled air is investigated and the amount of eliminated carbon dioxide and consumed oxygen is judged by the difference in the composition. The inhaled air (anywhere in the world and at any altitude up to 12 and even 15 kilometres above sea level) has the following composition: 20.94 per cent O_2, 0.03 per cent CO_2 and 79.03 per cent N_2 (including argon and the other inert gases). If, for example, the exhaled air contains 16.74 per cent O_2 and 3.53 per cent CO_2 each 100 cm.^{3} of air taken in through the lungs has 4.2 cm.^{3} of consumed O_2 and 3.5 cm.^{3} of eliminated CO_2.

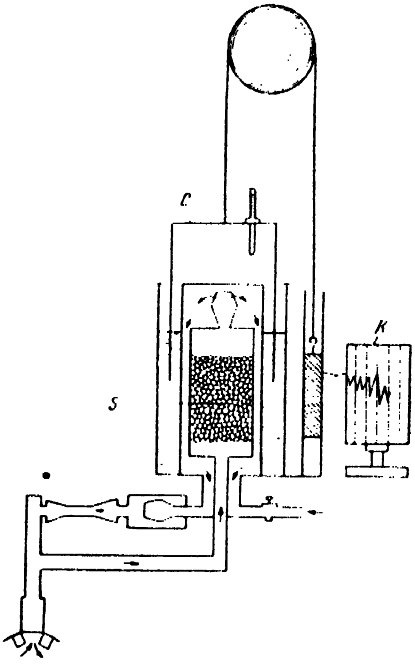

Fig. 143. Installation for measuring gas metabolism in man (after Krogh).

Inhaled air (its movement is shown by arrows) passes under cylinder of spirometer *(C)*, which is filled with oxygen (or air) beforehand. Eliminated carbon dioxide is absorbed by soda lime *(S)*. Oxygen consumed is measured by the lowering of the spirometer cylinder, which is recorded on kymograph *(K)*.

The instruments for studying the gaseous exchange differ quite a good deal because the gaseous exchange in man and in animals is determined under various conditions and at different periods of time—from a few minutes to 24 hours and more.

The most accurate method for studying gaseous exchange in protraced experiments, especially in animals, is the chamber method.

The simplest modification of the chamber method (Fig. 141) consists in the fact that the investigated animal is placed in a hermetically sealed ordinary metal, more rarely glass, chamber of a certain volume (pneumatic chamber). Before the experiment the composition of the chamber air is determined by analysing a sample of it in Haldane's gas analyser. Given the volume of the chamber and the composition of the chamber air it is not hard to compute the amount of oxygen and carbon dioxide contained in the chamber before the experiment.

The animal is placed in the chamber and samples of the chamber air, changed as a result of the animal's respiration, are taken and analysed at certain intervals of time. Since the exact volume of the chamber is known the content of oxygen and carbon dioxide is computed and the amount of oxygen consumed and carbon dioxide eliminated during the experiment is judged by the difference from their content in the beginning of the experiment. Since these values are known it is possible to compute the respiratory quotient and the output of energy in calories.

The drawback of the pneumatic chamber method is that the experiment cannot be continued very long because carbon dioxide accumulates in the chamber and the partial pressure of oxygen drops.

The chambers built after the same model but equipped with a device for ventilating the air are better; in these chambers air is sucked in during the entire experiment through special absorbing reservoirs in which the accumulated carbon dioxide is absorbed in an alkaline solution. The elimination of carbon dioxide leads to a drop in the pressure within the chamber. This is made use of to replace the carbon dioxide in the chamber by oxygen from special gas-meters. In this case the consumption of oxygen is determined by its diminution in the gas-meters, while the production of carbon dioxide is found by titrating the alkaline solution in the absorbers before and after the experiment. This chamber makes it possible to continue the experiment for a very long time. A very convenient chamber model was developed by M. Shaternikov, I. Sechenov's pupil (Fig. 142).

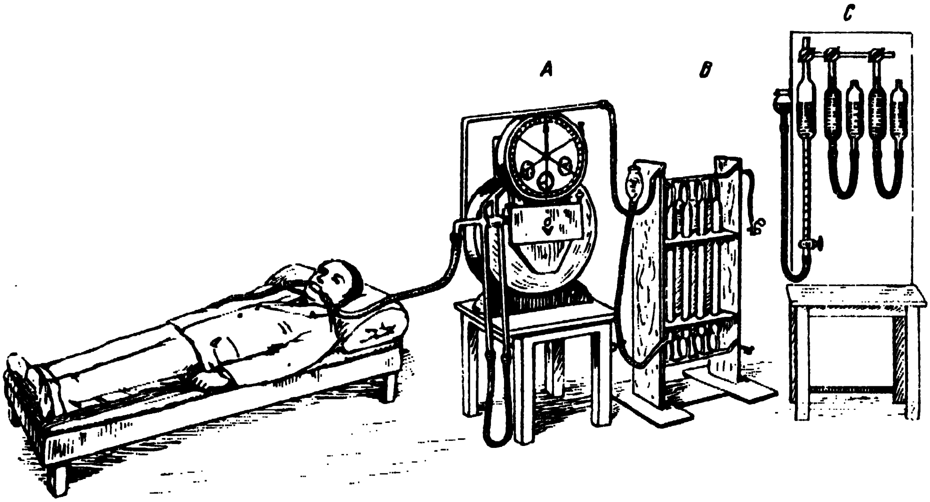

Fig. 144. Installation for determining gas metabolism in man (after Zuntz-Haldane). Man lying on couch exhales through gas-meter (*A*): dial hand makes it possible to measure amount of air passing through gas-meter. Special valves, through which examined person breathes, separate inhaled air from the exhaled and lead all exhaled air only through meter. A small portion of exhaled air is collected in special containers (*B*). Air collected in containers is subsequently analysed in Haldane's apparatus (*C*).

A system of carbon-dioxide absorbers and a gas-meter (spirometer) filled with oxygen are often used for determining the gaseous exchange in man; the respiratory passages of man are connected with this system by a mask which covers the nose and mouth, or by a mouth valve and a nose clamp (Fig. 143). The consumption of oxygen is judged by its decrease in the gas-meters or in the spirometer, while the production of carbon dioxide is computed by the change in its content in the absorbers (by titration or accurate weighing of the absorber). All these systems of instruments for studying gaseous exchange are known as *closed systems*.

The chamber methods are very convenient for experimenting on animals in the laboratory, but are hard to use in the clinic and under working conditions for studying the gaseous exchange in man. The methods of study with the aid of *open systems* (Figs. 144 and 145) are widely used in this case.

In these methods man inhales external air through the mouth or through the mouth and nose with the aid of a mouthpiece or a special mask equipped with valves. The valves make it possible to direct all the air exhaled during a certain period of time into a gas-clock or gas-meter where its amount is accurately measured. Frequently (especially in studying the gaseous exchange during work) the air is first collected in Douglas bags and then measured by being passed through a gas-clock. At the same time samples of the exhaled air are taken to analyse the content of oxygen and carbon dioxide in it. Since the amount of the expired air and the composition of the inspired (external) and expired air are known it is not hard to compute the amount of oxygen consumed and carbon dioxide produced during the time of the experiment.

Here is an example. A man exhaled 5.2 litres of air in one minute, the exhaled air containing 16.23 per cent oxygen and 4.13 per cent carbon dioxide. From each 100 cm.^{3} of air passing through the lungs the organism has consumed $\underset{\text{external air}}{20.94\text{ ml.}} - \underset{\text{exhaled air}}{16.23\text{ ml.}} = 4.7\text{ ml.}$ (or 47 ml. per litre) of oxygen

Since the pulmonary ventilation equalled 5.2 litres the consumption of oxygen per minute equals:

$$47\text{ ml.} \times 5.2 = 244.4\text{ ml.}$$

Consumption of carbon dioxide per 100 cm.^{3} of air equals:

$$\underset{\text{exhaled air}}{4.13\text{ ml.}} - \underset{\text{external air}}{0.03} = 4.1\text{ ml. (41 ml. per litre)}$$

Consumption of carbon dioxide per minute equals:

$$41\text{ ml.} \times 5.2 = 213.2\text{ ml.}$$

We now determine the respiratory quotient (in round figures)

$$\frac{CO_2}{O_2} \cdot \frac{213}{244} = 0.87$$

For the respiratory quotient of 0.87 the caloric value of one litre of oxygen (Table 16) corresponds to 4.88 large calories. Hence, for the consumption of 244 ml. (0.244 lit.) of oxygen per minute the caloric value corresponds to 4.88 large calories × × 0.244 = 1.19 large calories. The energy output is, thus, 1.19 large calories per minute or 1,714 large calories in 24 hours.

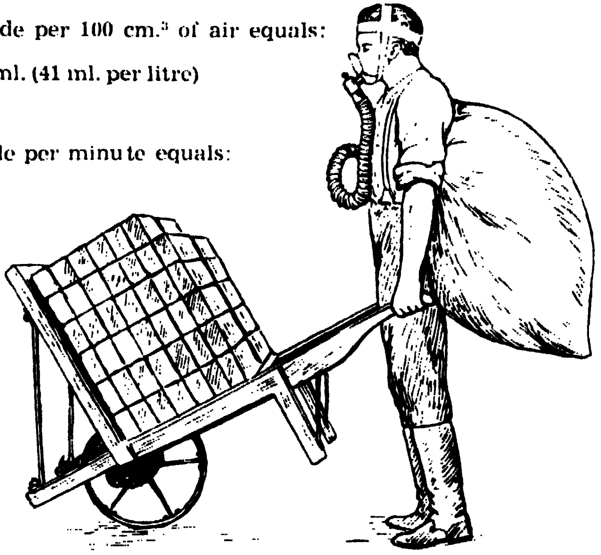

Fig. 145. Determining gas metabolism energy output—during work (same method is often used in determining gas metabolism during rest).

All air exhaled by person passes into Douglas bag. This is made possible by the fact that the person breathes through a mask hermetically pressed to face or through mouthpiece equipped with valve (in this case the nose is stopped up). Exhaled air passes through tube into bag. At end of experiment, lasting a definite period of time, amount of exhaled air is measured by gas-meter. Sample of air taken from bag is analysed for its O_2 and CO_2 content.

The study of the gaseous exchange in man is of considerable practical importance. It is used for a number of purposes, primarily, in investigating dietary requirements. Nutrition must cover the energy needs and in a growing organism must exceed them. The dietary requirements are (see p. 366), therefore, always based on studies of energy output established by determining the gaseous exchange. In addition, a number of problems connected with changes in physiological functions in labour processes and in sports are also solved by the method of determining the gaseous exchange. During considerable muscular effort the gaseous exchange is sharply modified (Fig. 145).

The study of the gaseous exchange acquires considerable importance in the diagnosis of certain diseases, nutritional disorders, etc. Finally, the study of the gaseous exchange is also very important as a method which characterizes the intensity of the body's activity under various conditions of the external environment (for example, climate, diet), during the sleeping and waking hours, etc.

The study of all these influences requires the knowledge of the main laws governing the total value of energy expenditures of the body.

Energy Output at Rest and Basal Metabolism

In the sixties and seventies of the 19th century Bidder and Schmidt found that the energy output in man at rest was quite constant. This was confirmed by a number of investigators in the beginning of our century. It appears that the lowest energy output in man and animals is observed outside of muscular activity and food intake and at a temperature of the environment corresponding to the minimal activity of the thermoregulating mechanisms. The relatively constant level of energy expenditure under the aforesaid conditions is known as the *basal metabolism.*

To determine the basal metabolism the gaseous exchange is studied in the morning hours about 14 to 16 hours after the last meal (temperature of the room 20 to 22°). The individual whose basal metabolism is being determined is requested to lie quietly in any convenient position. Basal metabolism is best determined in bed immediately after awakening. The examination lasts 10 to 15 minutes and is usually repeated, sometimes several days running, if surgery, for example, an operation on the thyroid. is to be decided upon.

The statistical analysis of extensive material determining basal metabolism in healthy people shows that people of the same sex, height, weight and age have approximately the same basal metabolism and that it varies no more than 10 to 15 per cent. It appears, furthermore, that basal metabolism is proportional not so much to the weight of the body as to its total surface area. Thus, in small animals whose body surface per unit of their weight is much greater than in large animals basal metabolism in proportion to body weight is several times as high. This can be seen in Table 17.

Table 17

Energy Output in Different Animals per 1 m.^{2} of Surface and 1 kg. of Body Weight per Hour

Animal	Body weight (kg.)	Heat production in 24 hours (in large calories)	
		per 1 kg. of body weight	per 1 m.^{2} of body surface
Horse	441	11.3	948
Pig	128	19.1	1,078
Dog	15.2	51.5	1,039
Rabbit.....	2.3	75.1	776

The energy output per one kg. of weight greatly varies for animals of different weight, but calculation per unit of body surface (1 m.^{2}) yields rather close results for animals sharply differing in body weight.

This circumstance gave the French physiologist C. Richet and the German physiologist M. Rubner reasons to formulate the so-called "surface-area law," according to which the energy output (at complete rest) per unit of body surface is relatively constant. These and subsequent investigators, however, interpreted the established dependence as an absolute physical law since they believed that at rest the energy output depended only on the loss of heat from the body surface.

This interpretation of the surface-area law is incorrect. The dependence of the intensity of metabolism on the body surface arose in the course of evolution in which the mobility of the animal, the rate of its metabolism, its food requirements, etc., each played a definite part.

There are many exceptions to the surface-area law which are explained by biological peculiarities of animals; for example, with the same body surface the metabolism in wild, more mobile animals is always higher than in domestic animals; in the denizens of the tropics it is lower than in those of the central zone and of the polar regions, etc. As we shall show later (p. 363) this is closely connected with the regulation of metabolism by the cerebral cortex; this regulation establishes a constant dependence of the body's energy output on the various factors of the environment.

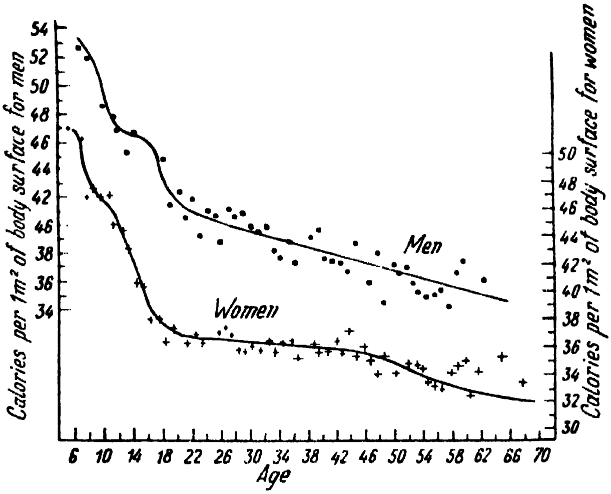

Fig. 146. Changes in energy output studied under conditions of basal metabolism with reference to age.

Ordinate on the left shows scale of energy output in large calories per 1 m.² of body surface for men; right same for women. Dots and crosses show results of individual experiments for men and women respectively.

Certain changes in the energy output (per 1 m.² of body surface) are observed in connection with age (Fig. 146 and Table 18).

Table 18

Basal Metabolism Averages in Large Calories per 1 m.² of Body Surface per Hour (after Du Bois)

Age in years	Basal metabolism averages (large calories)	
	in men	in women
14–16	46.0	43.0
16–18	43.0	40.0
18–20	41.0	38.0
20–30	39.5	37.0
30–40	39.5	36.5
40–50	38.5	36.0
50–60	37.5	35.0
60–70	36.5	34.0
70–80	35.5	33.0

The statistical study of the data yielded by the investigations in basal metabolism has made it possible to determine certain averages of energy output at rest for men, women and children of different weights and ages. These tables developed by Harris and Benedict are widely used, especially in clinical practice. By using these tables or by calculating the body surface according to the nomogram (Fig. 147) and multiplying this value by the corresponding figures (Table 18) it is possible to compute for each individual the average value of energy output at complete rest on the condition that all the requirements of determining basal metabolism are observed.

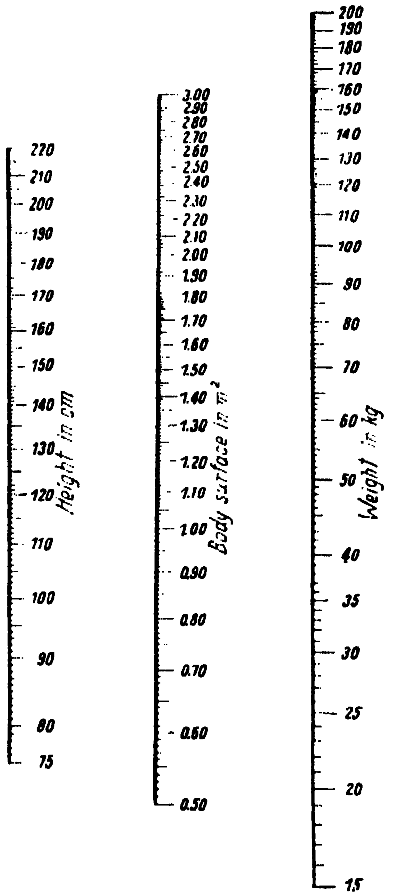

Fig. 147. Nomogram for determining body surface. Body surface of given subject is found at the point where straight line, connecting points corresponding to his height and weight, crosses middle scale.

The use of these tables is warranted only for comparing the data characterizing the energy output of different people at complete rest under standard conditions of investigation. Experience shows that the external environment (for example, climate, temperature, barometric pressure, lighting) and the internal environment, as well as the different forms of bodily activity outside the time the basal metabolism is determined (for example, athletic training, dietary changes, etc.), may cause considerable deviations from the aforesaid standards.

Both the constancy of basal metabolism and its variations are explained by cortical regulation of metabolism.

The studies of K. Bykov and his associates (R. Olnyanskaya, A. Slonim et al.) have shown that a formerly indifferent stimulus, for example, the sound of a metronome or a bell used at the same time as factors which increase metabolism, for example muscular activity, food intake, an injection of thyroxin, etc., leads to the development of stable conditioned metabolic reflexes. The formerly indifferent signals become active metabolic stimuli. Time may be a similarly important stimulus. Experiments show that the increase in metabolism at certain times of day is connected with the dietary regime; the rise in metabolism at these times of day is independent of the actual food intake. Thus, the *rate of basal metabolism depends on the total activities of man or animal.*

The mode of the body's activity, nutrition or muscular work repeated at definite times of day lead to the development of a complex reflex bond (cortical pattern, Chapter 62) in response to the total influence exerted by the food intake, muscular activity, temperature, etc. Under constant conditions of existence the basal metabolism (at certain times of day) is also constant. Experiments show that under constant conditions of investigation (room, time of day) it is possible sharply to change the temperature of the external environment (which generally considerably affects metabolism) without altering the basal metabolism. The elaborated cortical bonds, which affect metabolism, produce a much stronger effect here than the special factors on hand. The constancy of basal metabolism must, therefore, be regarded as depending on the conditioned reflexes to the stereotype life pattern developed under the ordinary living conditions which are in some measure reproduced when the so-called basal metabolism is being investigated. It follows that the very term "basal" metabolism is only conventional and does not reflect the essence of the matter.

The constancy of metabolism studied at definite hours and under definite physiological conditions may depend, primarily, on strictly constant habits. Very careful observations have shown basal metabolism to be strictly constant over a period of many years (Benedict). But this constancy in basal metabolism, like its certain variations under changed conditions of investigation, depends on the nature of the signal stimuli acting on the body under definite conditions and at definite times of day, i.e., on the nature of the cortical regulation of metabolism (p. 363).

Dependence of Energy Output on the Organism's Nutrition. Specific Dynamic Action of Food.

The rate of metabolism is directly related to the processes of nutrition. It is influenced by individual meals, the total amount of substances taken in with the food and their qualitative composition.

The so-called Pflüger's postulate had for a long time played a big part in the theory of energy transformations in the cells and tissues. According to this postulate the metabolism in the cells and tissues (consequently, in the body as a whole) does not depend on the supply of foodstuffs, but exclusively on the physiological state of the tissues. This postulate, progressive for its time because it replaced Liebig's grossly mechanistic ideas of the complete dependence of vital activity on nutrition, now proves absolutely incompetent with respect to the body as a whole.

Our ideas of the relationship between the income and expenditure of substances spring from the concept of the unity of processes of assimilation and dissimilation. Very frequently an increased expenditure of foods leads to their increased consumption, while limited expenditure leads to limited consumption. Thus, for example, limited nutrition involving external signals connected with an impossibility of obtaining food leads to a sharp decrease in the body's activities and to an increase in the sleeping periods which in some species of animals prepares the body for winter or summer hibernation.

Every food intake causes a rise in the metabolism of the body which is in a state of muscular rest. This rise in metabolism, which results from the intake of food and is observed even under the strictest conditions of rest, has been termed the *specific dynamic action of food.*

The greatest specific dynamic action is produced by the consumption of proteins. The increase in metabolism may, in this case, reach 30 to 40 per cent of the total energy value of the consumed protein. The metabolic increase does not begin immediately the protein food is consumed, but 1.5 to 2 hours later, reaches its maximum within 3 hours and continues for another 7 to 8 hours after the meal. For carbohydrates the value of the specific dynamic action is much lower and reaches only 4 to 6 per cent of the energy value of the substance consumed by the body; an increase in total metabolism is observed in this case only for a period of 2 to 3 hours after the meal. The effect of the specific dynamic action of fats differs in various individuals. In rats consumption of fats causes an increase in the metabolism, in rabbits—a drop. A very slight increase in metabolism after the consumption of fat is characteristic of man. In the usual mixed diet the expenditure of energy for the specific dynamic action of food constitutes 150 to 200 large calories, i.e., 10 to 12 per cent of the basal metabolism.

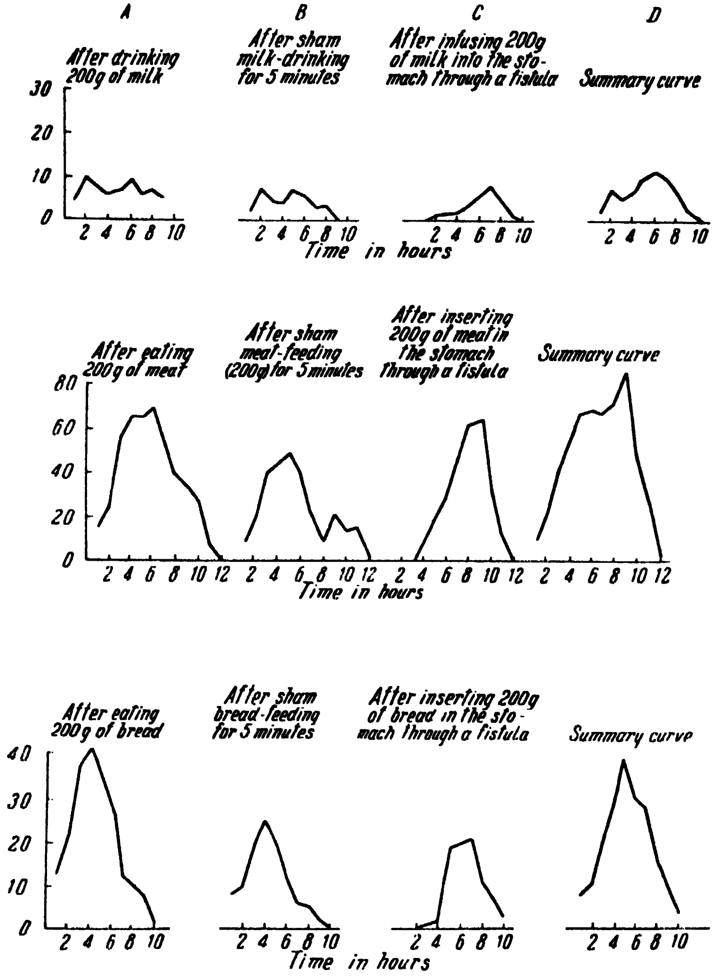

Fig. 148. Surplus oxygen consumption (compared with metabolic rate before food intake).

A—after drinking 200 gr. of milk (top), eating 200 gr. of meat (middle) and 200 gr. of bread (bottom); B—after sham feeding with milk, meat or bread; C—after inserting 200 gr. of meat or bread or pouring 200 gr. of milk into stomach; D—summary curves B and C. Abscissa shows time in hours (compare with Fig. 111) (after R. Olnyanskaya).

The reasons for the specific dynamic action of food are not clear as yet.

The old authors ascribed great importance to the "stimulatory" action of proteins and the products of their conversion on cellular processes. This also holds true of the transformations of nitrogenous substances in the liver and the tissues. The energy output for the functions of the muscular and glandular apparatus of the digestive tract is, apparently, also of some significance. The specific dynamic action in the consumption of carbohydrates is connected with energy outlays conditioned by the change of glucose into glycogen. All these factors belong only to the direct influence of certain consumed foodstuffs on the energy output; in addition, we must consider the great importance of the act of eating as a signal stimulus of the ensuing process of digestion and tissue processes of assimilation.

Proceeding from this K. Bykov's associates used Pavlov's method of sham feeding to analyse the specific dynamic action of food. It appears that sham feeding alone, i.e., actually the act of eating alone with no food entering the organism, could bring about an increase in metabolism lasting for many hours. In this case the total increase in metabolism reaches 50 to 60 per cent of the entire specific dynamic action of food observed when it is really eaten. The same food put into the stomach through a fistula (unnoticed by the dog) causes a small rise in metabolism (about 40 per cent) compared with normal eating which, moreover, occurs later than in sham feeding (Fig. 148).

In summing up the increase in metabolism observed in the experiments with sham feeding and the metabolic increase occurring when the food is placed into the stomach through a fistula we get a figure very close to the usual specific dynamic action of the given type of food (compare Fig. 148 with Fig. 111 which shows a synthesis of Pavlov's curves of gastric juice secretion).

On the basis of these data we are warranted in saying that both nervous mechanisms and humoral factors are of importance in the specific dynamic action of food. The former are connected with the act of eating, the latter—with the absorption of the products of digestion into the blood and with the processes of assimilation of the substances by the tissues of the body. A conditioned reflex developed in the course of individual life lies at the base of the reflex nervous phase of the specific dynamic action of food. By repeating sham feeding many times running we observe the fading of this reflex; sham feeding ceases to produce a rise in metabolism. This is, probably, also due partly to the fact that with no stomach distention and absorption repeated sham feeding causes the formation of a conditioned inhibition (Chapter 60) owing to which metabolism no longer rises after feeding. In dogs grown on dairy and vegetable food sham meat-feeding causes no increase in the gaseous exchange.

The observations made in the studies of the gaseous exchange in newborn children before the first feeding are very important. It appears that sucking on an empty nipple may cause immediately after birth a considerable rise in metabolism lasting an hour and longer though the nipple was sucked for only 8 to 10 minutes (N. Arkhangelskaya). The influence of the act of eating on metabolism is, obviously, an unconditioned, inborn reflex. In the course of a number of feedings this effect grows, which indicates an addition of conditioned-reflex influences, both stimulating and inhibiting, on the processes of metabolism.

The rate of basal metabolism varies considerably with the time of day the animals are fed (feeding regime). If the monkeys usually fed three times a day in captivity are given only one meal a day during the evening hours (the daily ration retained) a decrease in basal metabolism, determined in the morning, is observed several days later. Despite the fact that in this case, i.e., single evening meal, the monkeys consume much more food 14 hours before determination of their metabolism, the latter is lower in the morning. Here we, apparently, have an extinction of the conditioned reflex for the meal no longer given during the morning hours. By changing the feeding regime we can, consequently, alter the metabolism at will and either increase or decrease it.

A decrease in total metabolism is observed in insufficient feeding. This drop is evident even in small dietary limitations. A specially low metabolism is observed in very deficient rations.

It is very important to note that a decrease in metabolism is not coincident with a loss of body weight; consequently, the weight of living tissue is not the only factor determining the rate of metabolism. Of great significance here, as previously stated, is the falling out of the specific dynamic action of food, including its complex reflex phase.

A considerable decrease in metabolism during complete starvation has been established by a number of investigators. V. Pashutin and his pupils, Benedict et al., have made an outstanding contribution to this problem. Table 19 shows the changes taking place.

Table 19

Changes in Daily Energy Output and Loss of Weight in Starvation

Duration of starvation in days	Body weight (in kg.)		Daily energy output (in large calories)		Energy output per kg. of body weight per day (in large cal.)		Energy output per square metre of body surface per day	
	before starvation	last day of starvation	before starvation	last day of starvation	before starvation	last day of starvation	before starvation	last day of starvation
41	62.8	46.0	1,790	780	26.6	17.0	1,039	529
30	57.9	45.5	1,525	935	27.5	20.5	905	679
16	43.5	36.0	1,278	917	28.4	25.4	929	722
5	67.0	63.1	2,220	1,970	33.2	31.2	—	—

It is important to note that starvation reduces the functions of a number of organs, for example, the heart rate, the respiratory volume and respiratory rate; the mobility of the body and its muscular activity change sharply. Thus, a decrease in the amount of the work done and inhibition of the conditioned-reflex influences developed during the lifetime of muscular activity and food intake lead to changes in the rate of metabolism.

The foregoing sheds light on the mechanism of the so-called physiological starvation occurring in some animals in connection with seasonal feeding changes. It is well known, for example, that some animals (bear, badger) fatten very much in summer and autumn, and though they do not fully hibernate in winter they nearly cease to eat and live on the accumulated fat. These animals refuse to eat in winter even in captivity. In this case we are dealing with a sharp inhibition of the responses to food stimuli and metabolism takes place at the expense of endogenous feeding, which V. Pashutin termed "physiological" starvation. If the awakened animal is fed during this winter period the specific dynamic action of food either sharply diminishes or drops out completely.

Energy Output in Muscular Activity

The heart, the respiratory muscles, the kidneys, the liver, etc., never cease functioning even when the body is at complete rest. The skeletal muscles retain a certain tension even when the musculature is relaxed in a horizontal position, particularly during sleep. It is assumed that of the total metabolism 4 to 6 per cent goes for the heart muscle, 4 to 6 per cent for the kidneys, 20 to 30 per cent for the liver and the organs of the digestive tract, 2 to 5 per cent for the nervous system and 40 to 50 per cent for the skeletal muscles.

In muscular activity the muscle metabolism sharply increases. Compared with the metabolic rate during lying at rest a quiet sitting posture causes a 12 per cent increase in metabolism, standing—a 20 per cent increase, slow walking—an 80 to 100 per cent increase, and running—a 400 per cent increase. Very vigorous muscular work may increase metabolism tenfold compared with rest. Certain athletic activities, for example sprinting, rowing and cycling may cause even greater energy output per minute (up to 22 large calories).

There is a definite correlation between the amount of work done in kg-m. and the amount of energy spent on it. This impelled physiologists to study the efficiency of man and animals.

In order to compute the efficiency it is necessary to know the exact amount of work done in kg-m. and the amount of energy in calories spent on this work.

The efficiency (K) is computed by the following simple formula:

$$K = \frac{W}{H},$$

where W is the amount of work done in terms of heat (and considering the following mechanical equivalent of heat—one large calorie corresponds to 427 kg-m. of work), and H is the total energy output in calories required to do the work. The highest efficiency of man appears to be 20 to 25 per cent.

The determination of the value of W for most of the work done by man presents practically insurmountable difficulties because it is impossible to measure his external work in kg-m. with any degree of accuracy. Besides, the efficiency of man, even when it is possible to compute it with satisfactory accuracy (for example, in lifting a weight, turning a wheel, laying brick), takes into account only the sum total of the energy changes in the organism in connection with the external work done and hardly reveals its physiological peculiarities. The comparison of the nature and structure of the muscular activity of man with the energy spent on it warrants the assumption that the most economical in this respect is the work done by the large muscle groups in which movements rhythmically follow each other. Thus, for example, turning a wheel is much more economical than lifting and lowering a weight. This is due to the fact that rotatory movement does not require a change in the direction of the movement, while the latter is connected with a stop and a new starting impulse which requires an additional output of energy to overcome inertia. Of considerable importance to the energy value of man's work is the rate at which it is done. For each type of muscular work, for example, walking, running, lifting and lowering weights, cycling, hammering, filing, etc., it is possible to determine the optimum rate, i.e., a working rhythm with the lowest energy output per unit of work. However, the given optimum-energy rate of work cannot be regarded as the most advantageous for performing any particular labour because it does not take into consideration the complex conditions under which fatigue develops.

The energy expenditure entailed in muscular work, though amenable to precise measurement, cannot serve as a criterion of the strain or the fatigue the work produces. Every form of muscular activity is composed of two elements. One of these is the muscular activity proper; it may be conditionally termed "effort of movement" (it is often called dynamic); this includes the muscular efforts connected with moving loaded or unloaded extremities. The second element is the "effort of support" (frequently designated as static), i.e., effort designed at supporting a weight, maintaining the balance of the body. In muscular movements similar in structure, for example, in moving some load by hand in a horizontal plane, as the rate of movement decreases the relative role of the efforts of the first type diminishes while the role of the efforts of support increases. Numerous studies in gaseous exchange show that in this case the energy output increases insignificantly, while the work becomes very tiresome.

Training for a given type of muscular activity is of enormous importance to the energy output for the work done. Due to systematic training the energy output for work done decreases because the work involves fewer muscle groups, the rate of respiration and circulation and the chemical dynamics of the muscles change.

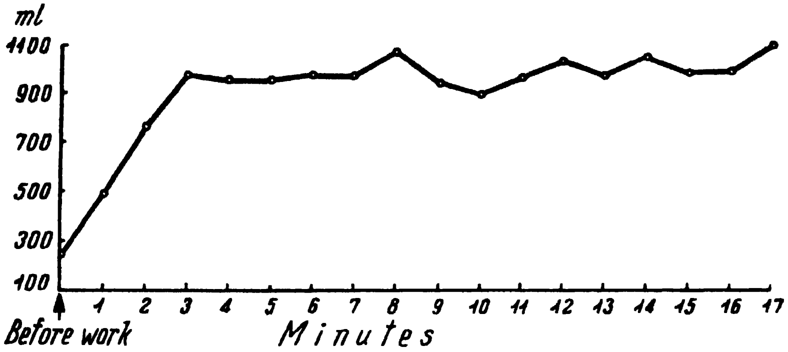

Fig. 149. Rate of oxygen consumption (in ml. per minute) during protracted moderately hard physical work (after A. Slonim).

Numerous studies of gaseous exchange during muscular work of varying intensity have shown that the exchange not only increases during work, but continues at a higher rate for some time afterwards. These phenomena, which have been termed the period of recovery after muscular work, must be considered in connection with the chemical changes occurring during muscular contraction.

It is pointed out on page 462 that a complex cycle of anaerobic changes of various substances occurs in the skeletal muscles and that these transformations lead to a liberation of energy which can be changed into mechanical energy, i.e., into work done by the muscles. The substances (chiefly lactic acid) formed in anaerobic processes as a result of the split up of high molecular compounds are oxidized by the oxygen brought to the muscles by the blood. This leads to the liberation of much greater quantities of energy than is the case in anaerobic transformations, part of this energy being used for resynthesizing the substances converted during the anaerobic phase.

The amount of oxygen required to oxidize all the products of anaerobic metabolism formed per minute of work is designated as the *oxygen requirement*. When the amount of oxygen consumed by the body per minute of work corresponds to the oxygen requirement the concentration of underoxidized products in the blood and in the muscles does not increase during the work (Fig. 149). In this case a constant rate of oxygen consumption is established and maintained throughout the duration of the muscular effort on approximately the same level. Work in which this constant rate is achieved can frequently be done for long periods of time.

The constant rate of oxygen consumption depends on the intensity and nature of muscular work; in a 1 to 2 kilometre run at top speed it reaches approximately 3 to 4 (up to 4.5) litres of oxygen per minute.

The satisfaction of the oxygen requirement depends on the functions of pulmonary respiration and circulation; during the first minutes of work (2 to 3 minutes) consumption of oxygen lags behind the oxygen requirement. This is due to the fact that the volume of respiration and the minute volume of the heart cannot at once accommodate themselves to supplying the muscles with the amount of oxygen corresponding to the oxygen requirement. That is why underoxidized products of metabolism accumulate during the initial stage of work and must be oxidized after work. An additional amount of oxygen must be spent after work to oxidize these substances; this additional amount of oxygen is known as *the oxygen debt* (A. Hill).

At one time it was believed (A. Hill) that all compounds which could not be oxidized at the initial stage of work (before the supply of oxygen to the muscles and the oxygen requirement were equalized) remained unoxidized as long as the work lasted and that the oxygen debt was liquidated only after work. This idea proved wrong, however, because part of the oxygen debt is liquidated while the work is still being done. In addition, the higher oxygen consumption after work is connected not only with the oxidation of the products of anaerobic disintegration accumulated in the organism during work, but also with the changed metabolism in the musculature itself. The oxidative metabolism in the musculature (probably, also in the liver) sharply increased during work, does not decrease to its pre-work rate immediately upon the termination of work, but gradually. If the muscular work is so vigorous that the consumption of oxygen lags behind the oxygen requirement throughout the work period, higher oxygen consumption continues after its termination for the purpose of paying-off the oxygen debt.

Data characterizing various forms of muscular activity in accordance with their recovery periods are given in Table 20.

Table 20

Oxygen Consumption During Muscular Work and During the Recovery Period

(After G. Konradi, A. Slonim and V. Farfel)

Nature of work	Duration of work (in sec.)	Consumption of oxygen during work (in litres)	Oxygen debt (in litres)	Duration of recovery period (in min.)	Proportion of oxygen debt to oxygen consumed during work (in %)
100-metre sprint.....	13.6–15.8	--	6.5–10.1	18	88–94
10,000-metre run	41.15	--	22.8	25	15
Forging hot metal ...	60	1.2–1.6	1.9–3.0	7–11	60–65
Hammering.........	120	1.1	0.4–0.5	6–7	25–30
Carrying bags.......	Indefinite time	1.5 (per minute)	3.5	9	...
Crating bread.......	Ditto	0.7 (per minute)	0.6	3	—

Several studies made by K. Bykov and his associates show an extraordinarily complex picture of alternations in the gaseous exchange of man and animals during muscular work; the changes are connected with factors of nervous regulation of metabolism. It appears that it is possible to develop a number of conditioned reflexes for gaseous exchange by combining signals formerly indifferent to metabolism (for example, sound and light) with muscular activity of a certain intensity. These facts obtained in a laboratory were subsequently verified in industry and in sports. Gaseous exchange in a worker with long experience is always lower when examined in a laboratory (standing in working posture) than in the shop (Fig. 150). On a workday when the shop is running the gaseous exchange is higher than on an off-day when there is no work in the shop. The gaseous exchange in a worker increases when he works on his own team; work on another team produces no such effect.

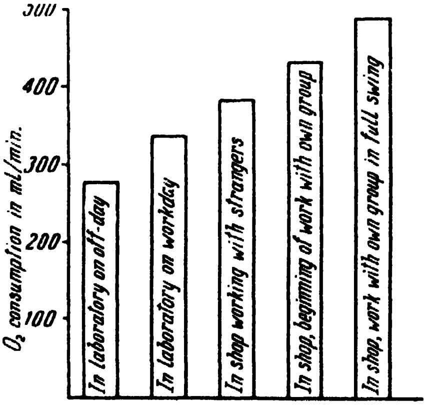

Fig. 150. Changes in oxygen consumption under influence of signal stimuli connected with industrial labour (after R. Olnyanskaya).

It has been shown that the signal stimulus connected with muscular work may increase metabolism not only when the subject is in a state of rest, but also when he is working. Facts corresponding to these data were established at stadiums in studying the pre-start condition familiar to athletes. The gaseous exchange increased in the athletes long before the beginning of competition and these phenomena were more pronounced in experienced athletes than in novices. It has also been shown that after a run of 30 metres the energy output in an athlete nearly reaches the rate required for running 100 metres if the athlete is suddenly stopped on the 30th metre while he intends to run 100 metres. Apparently, the run and the circumstances under which it is performed cause at the very outset the energy transformations required for covering the 100 metres. If different distances are run one after another the quantitative energy changes are modified accordingly; the transformations depend on the conditioned-reflex regulation of metabolism (both during work and recovery) in very vigorous muscular activity.

An analysis of the alterations occurring in the gaseous exchange under the effect of cortical impulses shows that we are dealing with profound changes in tissue metabolism due to the influence of the nervous system. These influences on the tissue processes are known as trophic influences, i.e., influences which without changing the working (functional) activity of a tissue are capable of changing the course of chemical processes in it. The functions of the endocrine glands are also of great importance since they offer definite pathways for the transmission of cortical influences to the tissue processes. Experiments have shown that extirpation of the thyroid or the suppression of its function by methylthiouracil lead to a disappearance of the cortical influences on the tissue metabolism; in these cases no conditioned reflexes are developed in response to thyroxin injections. The hormones of the hypophysis also play an important part in the transmission of cortical influences (R. Olnyanskaya).

Physiological Principles of Food Rationing

The physiological principles of rationing food are based on a number of concrete facts whose all-round analysis constitutes the subject matter of physiology of nutrition.

The energy, i.e., quantitative, aspect of nutrition is well grounded by studies of the gaseous exchange in people of different sex and age engaged in various work. These requirements are established as follows. The energy output of individual people is studied while they are at work; the data obtained are calculated over 8 hours, i.e., the entire workday. The value of the energy output made during work is added to the energy expenditures covering the activities of the human body outside working hours. This output, including the energy required for walking, standing and eating, constitutes an average of 1.5 large calories per one kg. of body weight per hour (while at complete rest and on an empty stomach the energy output roughly corresponds to one large calory per same unit of weight and time).

Calculations and studies show that for bedridden people the energy output constitutes about 1,600 to 1,700 large calories per day or 1 to 1.1 large calories per one kg. of body weight per hour. Sedentary life requires 2,500 large calories per day.

The following four groups (depending on nutritional requirements connected with particular occupations) can be tentatively established: first group—energy output 2,200 to 2,400 large calories per day (for people doing light work in a sitting posture); second group—energy output 2,600 to 2,800 large calories (for people doing light muscular work); third group—energy output 3,400 to 3,600 large calories (for people doing medium muscular work); fourth group—energy output 5,000 large calories and up (for people doing hard muscular work).

It stands to reason that all these values can be established only approximately; they constitute the energy basis of nutrition and must be verified by medical observation of various food rations (in children's institutions, dining-rooms, hospitals, etc.).

Some of the well-established energy output requirements are shown in Table 21.

The rationing of food must ensure not only the replenishment of the energy spent, but also the restitution of the protein losses; it must meet the requirements of growth at the same time providing a qualitative and quantitative composition of food which makes for the greatest efficiency and the best health. The question of the energy output and its replenishment is, therefore, only part of the enormous problem of nutrition.

The vitaminization of food, the dietary regime, the importance of palatability, the appearance of food and the conditions under which meals are taken (aesthetic and others) are problems that must be considered in the interests of the people's health and efficiency only on the basis of modern synthetic physiology.

The amount of food consumed by man is usually determined by a requirement, the subjective expression of which is called appetite. However, appetite, as an expression of the need for food, and the sense of hunger do not always fully correspond to the energy losses of the body. The rationing of food is, therefore, often the task of the physician both in the hospital and in prescribing a diet for the patient at home.

The amount of food to be consumed is established, on the one hand, on the basis of the data which characterize the daily energy output and, on

Table 21

Energy Output of People of Different Occupations, Students and Schoolchildren per Day (in Large Calories)

(Data of the Institute of Nutrition of the Soviet Academy of Medical Sciences)

People studied	Number of large calories
Industrial workers	
Metallists—turners and toolmakers	3,300
,, ,, in forge shop	3,700-4,000
,, ,, in rolling shop	3,500-4,100
,, ,, in foundry	4,000-4,500
Building workers	
Carpenters	4,500
Masons and bricklayers	5,000
Plasterers	3,900
Workers on state and collective farms	
Tractor-drivers	3,000
Ploughmen	4,700-5,000
Vegetable-garden workers	4,100-4,400
Threshers	4,700-6,000
Sheaf-binders	5,300-5,600
Mowers (hand mowing)	7,200
,, ,, (machine mowing)	3,600
Students and schoolchildren	
Students	2,800-3,000
Schoolchildren (12-14 years old)	2,400
,, ,, (8-11 ,, ,,)	1,900

the other hand, on the basis of the number of large calories liberated during the oxidation of the foodstuffs.

Some data concerning the most important foods are given in Table 22.

Table 22 makes it possible to compute the number of calories in any food combination and to choose a ration of the required caloricity. In order to gain weight the caloric value of the daily ration should be increased by 50 to 100 per cent as against the energy output. For example, sanatorium patients with a daily energy output of 2,000 to 2,500 large calories are given between 4,000 and 5,000 large calories in their food. To lose weight corpulent patients are given a ration covering half the daily energy output. In addition, in order to increase the energy output they are prescribed walks and a protein diet (the latter because of the specific dynamic action of the protein).

The liberation of very definite amounts of energy during the oxidation of various foods—proteins, fats and carbohydrates—enabled the German physiologist M. Rubner to put forward a hypothesis of the possibility of replacing some foods by others in proportions corresponding to the heat produced by their combustion. Thus, one gr. of carbohydrates, which yields 4.1 large calories, can replace in caloric equivalent one gr. of protein, which produces the same amount of heat when oxidized; one gr. of fat can replace 2.2 gr. of carbohydrates or proteins. The possibility of this replacement

Table 22

Caloric Equivalents of Certain Foods, Their Content of Proteins, Fats and Carbohydrates Considering the Extent to Which They Are Assimilated

(net-calories)

Foodstuffs	Number of large calories per 100 gr.	Content (in %)		
		proteins	fats	carbohydrates
Bread, black	237	6.8	0.7	48.2
,, white	264	6.3	0.4	58.6
Flour, rye	340	11.5	1.0	71.6
,, whole wheat	354	10.8	0.7	75.8
Rice	350	8.0	0.3	79.0
Macaroni	355	13.4	0.9	74.1
Barley	355	8.5	1.1	77.8
Beef, average fatness	320*	15.8	28.5	—
,, ,, ,,	250**	12.0	29.3	
Pork, average fatness	337*	16.3	30.1	—
Pork, average fatness	270**	13.4	24.2	—
Ham (depending on fat content)	230–320	15–13	14.4–29.0	
Fat	898	—	100.0	—
Butter	768	1.0	86.6	0.5
Herring	141*	19.5	7.1	—
,,	79**	11.2	3.9	—
Cod fish	104*	25.4	0.3	—
Potatoes, raw	73*	2.2	0.1	18.4
Cabbage	31*	1.6	0.3	5.6
Tomatoes, fresh	23	0.9	0.4	3.9
Beets, cooked	25	2.3	0.1	7.4
Milk, whole	69	3.3	4.0	5.0
,, skim	37	3.4	0.3	5.1
Cream	194	25.0	18.5	4.5
Cheese	420–460	26–29	34–36	0.3–4.0
Chocolate	610	12.9	48.7	31.3
Sugar	400	—	—	100.0

was termed the *law of isodynamy*. The physiological significance of this law is very limited because foods must not only ensure the energy requirements of the organism, but must also serve as the plastic material for building and restoring the tissue structures broken down during dissimilation. This pertains primarily to proteins (the protein requirements are considered in Chapter 30).

Fats and carbohydrates may in a certain measure replace each other, but only within the limits corresponding to the capacities of the digestive organs. An exclusively protein diet for man is extremely undesirable because it overtaxes the liver (deamination) and sharply increases the energy exchange. A sharp increase in the consumption of fats aimed at compensating for the energy output mainly by fat is also undesirable because it is responsible for acidosis produced by the formation of considerable quantities of unoxidized products of metabolism.

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* Edible part.

** Whole product.

Carbohydrates, of which 400 to 600 gr. are usually consumed daily, cover the main energy expenditures. The requirements in carbohydrates grow with the increase in the energy output.

Children and adolescents require relatively more food because in addition to covering their energy expenditures they need nutritive substances to ensure growth of the body. It is assumed that children up to 3 years of age require 3.5 gr. of protein per kg. of weight, from 3 to 15 years of age—2.5 gr. and from 15 to 17 years of age—2 gr. of protein per kg. of weight.

The total food requirements in calories may be expressed in the following figures: children 1 to 2 years of age—840 large calories per day, 2 to 3 years of age—1,000, 3 to 5 years of age—1,200, 5 to 7 years of age—1,400, 7 to 9 years of age—1,680, 9 to 11 years of age—1,920, 11 to 12 years of age—2,160, and 12 to 15 years of age—2,400 large calories. An allowance for muscular activity (approximately 50 large calories per hour of muscular activity) must be made in addition to these figures.

Three or four meals a day are considered the most rational dietary regime; eating more frequently results in a loss of appetite, less frequently—in a feeling of hunger. Dietary regimes for the sick constitute the subject matter of a special branch of science—dietetics.

Energy Output Under Influence of Various Environmental Factors

The influences on metabolism, which, as inborn unconditioned reflexes, cause changes in the chemical processes in the tissues, underlie all regulation of metabolism and, consequently, the energy output of the body. The factors causing variations in metabolism are: temperature of the external environment, food intake and the digestive processes, and muscular activity.

All these factors and the changes in the physiological state they produce are not isolated from each other in the process of the usual vital activity of the organism, but are closely interrelated. Each of these influences on metabolism combines with numerous signal stimuli which come into play in the vital pattern of man or animals.

Metabolic changes which are due to variations in the temperature of the external environment, as well as metabolism during muscular activity or after meals, can be observed from the moment of birth in newborn animals capable of independent movement and existence (for example, in kids and lambs, and partly in children). The entire complex regulation of metabolism is formed on the basis of these unconditioned reflexes and must be taken into consideration when the complex influences of the external environment on metabolism are analysed.

Under natural conditions of existence the rate of general metabolism very largely depends on a number of factors in the external environment of which the climatic and in particular the seasonal phenomena, as well as barometric pressure, are especially important.

The influence of external temperature on metabolism is known best. Under the influence of low temperature metabolism increases; with a rise in temperature metabolism decreases (Chapter 35). A prolonged stay of animals in an environment with a high temperature results in a lower rate of their basal metabolism and a decrease in the specific dynamic action of food. The opposite effect is observed under a protracted influence of low temperature. These variations also depend on cortical influences. For example, the destruction of the cerebral hemispheres in rats causes these adaptive metabolic changes to disappear.

The variations in metabolism under the influence of low barometric pressure are not so clear. Most of the studies conducted in mountains, during brief stays at high altitudes, have revealed an increase in metabolism and greater pulmonary ventilation. This phenomenon is, probably, due to the fact that the amount of air inspired at sea-level pressure takes up a larger volume at higher altitudes; the additional volume of the inspired air causes the respiratory musculature to do additional work.

The gaseous exchange in people permanently living in the mountains at high and medium altitudes (2,000 to 4,000 m. above sea level) is frequently lower than that at the sea level. This is especially pronounced in the southern latitudes of the Soviet Union, for example, in the mountains of Central Asia (Tien-Shan). Altitude acclimatization results not only in respiratory changes and changes in the respiratory function of the blood, but also in metabolic changes. Lower metabolism and diminished pulmonary ventilation were also observed in animals permanently living in mountains as compared with those living at the sea level.

In caisson work (work of divers) we deal with higher pressure. In these cases a stable increase in basal metabolism and in the metabolism during work is observed.

The influence of radiant energy on the energy output presents quite a complex picture. Thus, for example, ultraviolet radiation does not produce any noticeable variations in basal metabolism, but increases pulmonary ventilation by raising the sensitivity of the respiratory centre. A combination of ultraviolet radiation and cooling causes a considerable increase in metabolism, the ultraviolet radiation intensifying the production of heat. Long-wave infrared radiation causes a decrease in metabolism when the heat is moderate and an increase in metabolism when overheating the body.

The rays of the visible part of the spectrum cause different metabolic reactions in different animals. Most investigators observed an increased metabolism under the influence of lighting. This fact becomes intelligible from the point of view of Pavlov's physiology: lighting is a signal for greater activity for most animals with a diurnal mode of life and, especially, for man.

Studies made on simians have demonstrated that those who live under natural conditions in dense tropical forests (the green marmoset) show very little change (increase) in metabolism under the influence of lighting, while the metabolism of baboons, the denizens of woodless spaces, on the contrary, greatly increases under the action of lighting. The visible part of the spectrum is a very important stimulus which serves as the basis for complex conditioned and unconditioned neural connections with the most diverse functions of the body. It is characteristic that the evening twilight sharply reduces the metabolic rate at rest because it is a signal of the forthcoming muscular rest—sleep.

The gaseous exchange varies during different seasons. The nature of these variations is very complex and cannot be reduced to the influence of some one factor, for example, the temperature of the environment or the lighting regime. Thus, in the middle latitudes of the U.S.S.R., basal metabolism is highest in spring; a decrease is observed in summer; there is some increase again in autumn; in winter (December-January) the metabolic rate drops to its lowest.

These variations are observed in investigations of basal metabolism and, consequently, do not in any way depend on the thermal influences of the environment. In addition, the coldest period of the year is also attended by a sharp decrease in metabolism. This must be due to reduced winter-time motor activities of most people who do not engage in winter sports.

The climatic variations in the gaseous exchange, and in the basal metabolism in particular, are relatively slight. A stable decrease in basal metabolism is observed in the hot regions of the Soviet Union, for example, in the desert areas of Central Asia. Similar variations are noted in the southern regions of Asia and America. But in man, who has extensive opportunities for setting up an artificial climate and who has clothes and a dwelling, these variations are less pronounced than in animals; moreover, the tropical mammals have a lower basal metabolism than the denizens of the middle latitudes and the polar regions.

The development of conditioned reflexes in response to various factors in the external environment may sharply alter the metabolism of the body under different conditions of existence and activity. Natural conditioned reflexes to gaseous exchange are formed in response to the most diverse factors of the external environment which are of importance to the life of the organism. It has, thus, been established that the rate of gaseous exchange may be affected by the amount of space around the body—visual stimuli. For a number of animals, for example, sheep, the latter serve as a signal to follow the herd; a higher metabolic rate is always observed in sheep out in the open field (everything else being equal) than in the sheep-fold.

Placing gregarious animals (simians, sheep and many rodents) amongst their own kind causes a decrease in their gaseous exchange. This phenomenon is observed when all outward expression of muscular activity is excluded and is connected with changes in defensive and self-orienting reactions typical of these animals. It is proved by the fact that the introduction of an additional stimulus, which causes a defensive reaction (sound, wind, etc.) enhances the effect of the decrease in metabolism when the animal is put in a herd.

CHAPTER 35

HEAT EXCHANGE AND REGULATION OF THE BODY TEMPERATURE

Heat Exchange Between the Body and the External Environment

The life's processes in the body are accompanied by a continuous production of heat. The heat produced is also continuously lost by the body into the environment. The loss of heat is governed by purely physical laws, namely, heating the surrounding air by the body (*heat loss by convection*), radiating heat from its heated surface (*heat loss by radiation*) and spending heat on evaporating water from the skin and the respiratory tracts. In the last case the body loses the amount of heat which is known as the latent heat of evaporation and constitutes 580 calories per one gr. of water evaporated from the surface of the skin at 34° C. In addition, the body spends a certain amount of heat on heating the consumed food and water and inspired air.

An individual with a constant body temperature can exist only as long as the body loses into the environment in the three aforesaid ways the heat it produces about as fast as it is produced. The following figures show the proportions of heat losses in various ways at a 20° C temperature of the environment.

Heat Loss of the Organism (in %)

Convection	31.0
Radiation	44
Evaporation	21.5
Heating the food	1.5
Heating the air in the lungs	1.3
Heat lost with urine and faeces	0.7

If an individual's heat production equals his heat loss the body temperature remains constant. A change in the ratio between heat production and heat loss during a definite period of time leads to variations in body temperature. If less heat is lost than produced the temperature of the body rises; if more heat is lost than produced the body temperature drops.

Influence of Temperature on Physiological Processes

The life's processes in the animal are confined to the rather narrow limits of temperature of the internal environment—from 0° to 45 to 50° C. Only within this limit can the fermentative reactions, involved in metabolism, take place.

Man and the animals, especially the higher mammals with a constant body temperature, cannot endure wide temperature variations. For man a drop in body temperature below 22 to 25° C or its rise above 43° C are, as a rule, fatal. The nerve cells are particularly sensitive to temperature changes.

Temperature exerts a profound influence on the vital processes of the body. The physicochemical basis of this influence is the change in the rate of chemical reactions which is expressed in the so-called "Q_{10} Rule" (van't Hoff's). According to this law the rate of chemical reactions increases approximately twofold with a 10° rise in temperature (temperature coefficient Q_{10}). Van't Hoff's rule holds true only for monomolecular chemical reactions taking place *in vitro*. For complex chemical processes in the cells and tissues it has but very relative significance, particularly because the enzymes involved in all the chemical processes in the body are proteins which are inactivated when the temperature rises above a certain level; the dependence of the rate of fermentative reactions on the temperature may be expressed by a curve which rises to a certain limit—the optimum—and then drops.

Another factor limiting the significance of the temperature coefficient is the influence of the nervous system on the intensity of metabolism, especially clearly pronounced in mammals and birds in the phenomena of heat regulation. Shutting out the central nervous system (its destruction or anaesthesia) leads to a greater dependence of the intensity of metabolism on environmental temperature. The regulating role of the nervous system lies at the basis of the metabolic regulations in the animal. The nervous system maintains the intensity of the chemical transformations in the tissues despite their own temperature changes (i.e., despite the temperature influence on the rate of the elementary chemical processes). In the process of evolution this form of regulation becomes an important mechanism of maintaining the constancy of body temperature.

With the ever-growing relative constancy of the internal environment at the higher stages of the phylogenetic development of animals there also appears a constancy in body temperature. Only birds and mammals have a constant level of body temperature, though we can observe in a number of invertebrates and lower vertebrates elements of metabolic regulation and regular changes in behaviour (connected with changes in external temperature) which adapt the body to existence at different environmental temperatures. Thus, for example, in turtles during their winter hibernation the metabolism remains practically constant despite the fluctuations in the temperature of the soil from 1.5 to 9° C. This constancy is connected with the activity of the anterior parts of the central nervous system which regulate the winter hibernation. Extirpation of the anterior brain of turtles causes disorders in their winter hibernation and primarily changes in metabolism due to environmental temperature fluctuations.

Special motor activity aimed at maintaining the temperature of the hive at a constant level is observed in bees ("ventilator-bees").

Concept of Heat Regulation

Constant body temperature in animals is maintained by a special nervous mechanism which regulates a number of physiological functions. The complex regulation of the physiological processes, which balances heat production and heat loss in the body and, therefore, ensures the maintenance of a constant body temperature, has been termed "heat regulation" (thermoregulation). The animals that do not have this physiological mechanism are designated as *poikilothermal,* while those having this regulatory mechanism are known as *homoiothermal.* These designations have replaced the formerly used terms "cold-blooded" and "warm-blooded" animals.

Since poikilothermal animals have no heat-regulating mechanism they sometimes develop a very high body temperature (at high environmental temperatures or during muscular work). For example, in the sun the temperature of a lizard rises to 40°C, while the Mediterranean tuna fish develops a temperature of up to 36°C during fast swimming. The same is observed in insects flying on summer days. When not extensively heated by muscular work or by the sun the body temperature of poikilothermal organisms is close to the temperature of the external environment, exceeding it only by decimal fractions of a degree as a result of the heat liberated in the body. In their vital activity the poikilotherms, therefore, depend on the temperature of the external environment. With a drop in the environmental temperature they grow torpid due to a sharp decrease in metabolism caused by the lowered temperature of their own body tissues.

The homoiothermal organisms present an entirely different picture. Their vital activity is in large measure independent of the temperature conditions of the external environment because of their constant internal temperature. This constancy is due to the interaction of two interlinked, though aimed at opposite directions, processes—regulation of heat production and regulation of heat loss. Both these processes are conditioned by the activity of the central nervous system which regulates metabolism, circulation, perspiration and the work of the skeletal muscles; contractions of the latter, for example, lead to the production of heat.

Some animals are capable of temporarily changing from a homoiothermal to a poikilothermal state and vice versa. This transition is observed in all animals that hibernate in winter or summer, and these animals are, therefore, called *heterothermal.* Heterothermy is a characteristic acquired in the evolutionary process later than homoiothermy. This characteristic is of enormous importance for adaptation to unfavourable conditions (for example, shortage of food or water). Like all phenomena of heat regulation heterothermy is ensured by the activity of the central nervous system and is accompanied by a number of changes in the endocrine system.

Thus, a yellow gopher may be observed to sink into summer hibernation (as a result of adaptation) after being temporarily immobilized by having its extremities tied. Removal of part of a forest dormouse's cerebral cortex interferes with its winter hibernation. Finally, effectuation of the conditioned reflexes to cooling developed in a hedgehog leads to a drop in its body temperature and to hibernation. Hibernation is, in its turn, accompanied by a loss of many of the conditioned reflexes developed in the animal beforehand; they do not manifest themselves directly after its awakening. The animal can be awakened from hibernation by an injection of thyroxin or substances stimulating the sympathetic nervous system (benzedrine).

Animals sink into a hibernating state only when certain changes in the chemical composition of the tissues occur. These include, primarily, an accumulation of fat reserves. It has also been ascertained that the concentration of ascorbic acid in the blood and tissues plays an important part: animals (gophers) with a low ascorbic acid content do not lapse into hibernation. Variations in the environmental temperature are of no importance to the hibernation of most of the winter-hibernating mammals, though at high environmental temperatures their hibernation is considerably delayed and may not take place at all. Winter and summer hibernation is characterized by a practically complete disconnection of the nervous mechanisms of thermoregulation and by poikilothermy. However, excessive cooling of the hibernating animal leads to its immediate awakening.

Body Temperature and Its Normal Variations

Topography of body and skin temperature. The temperature of 37° C accepted as normal for the human body is only a mean figure with more or less pronounced regular deviations. It is very difficult to measure the mean body temperature, since that is really only the temperature of the blood in the right heart. The accepted mean temperature is, therefore, the temperature measured in the arm-pit or in the rectum. In the latter, however, it is 0.3 to 0.5° higher than in the former.

The highest temperature is observed in the liver where there is, apparently, the highest rate of heat production per unit of the organ's weight. Muscles show a high temperature during hard work. The blood in the pulmonary artery has a higher temperature than that in the left portion of the heart since much heat is lost in the lungs.

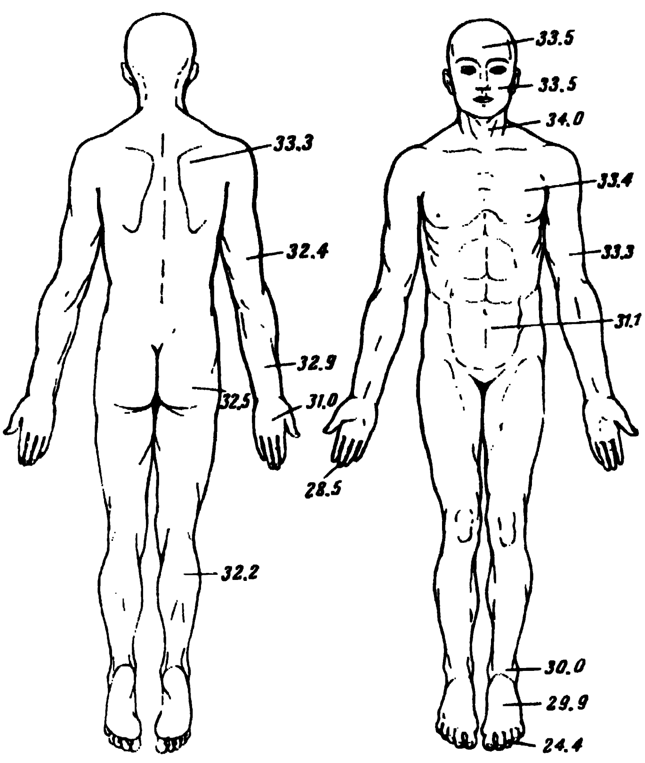

Fig. 151. Topography of skin temperature in man (after A. Slonim).

There are characteristic topographic differences in the temperature of the human skin. The highest temperature is observed in the skin of the trunk and the head. The temperature of the skin of the extremities lowers from the proximal to the distal parts. There is a stable difference in temperature between the portions of the skin covered and uncovered by clothing. It should be noted that in people inured to cold the temperature of the skin on the extremities is relatively higher and differs less from that of the trunk than in people who are not inured to cold; the temperature of their skin is determined, on the one hand, by that of the environment—the surrounding air, and on the other hand, by the amount of blood

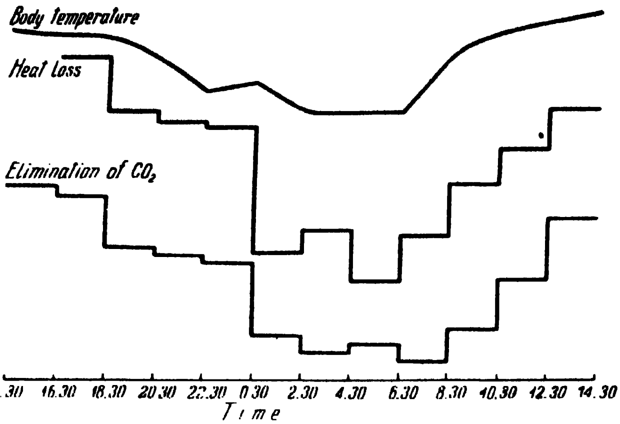

Fig. 152. Diurnal variations in body temperature, heat loss and carbon dioxide elimination (after A. Likhachov).

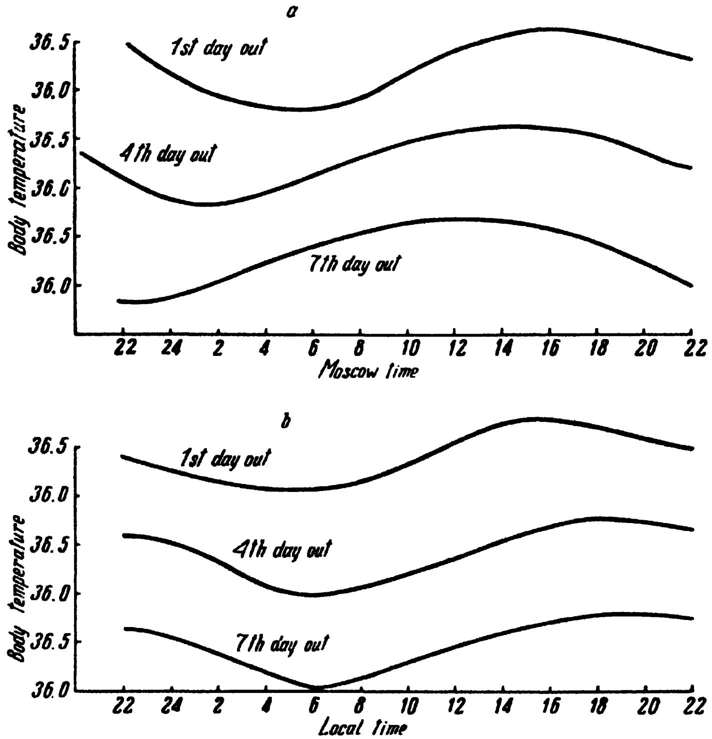

Fig. 153. Diurnal variations in body temperature of man travelling from Moscow to Vladivostok (after Kandror).

a—Moscow time *b*—local time

supplied to the skin (this amount is regulated mainly by the tone of the arterioles). Such characteristic topography of cutaneous temperature is typical of man and (Fig. 151) of simians; it is but weakly expressed in other mammals.

Diurnal variations in body temperature. The most regular changes in the human body temperature are its diurnal variations. Fig. 152 shows a diurnal curve of the human body temperature in comparison with the values of energy output—heat loss and metabolism (production of CO_2). The highest body temperature is observed during the day (between noon and 4 o'clock in the afternoon); the temperature gradually drops and reaches its lowest level (about 36° C) in the early morning hours (about 4 o'clock); after that the temperature begins to rise again and reaches a relatively high level by noon. These changes in the body temperature are characteristic of people everywhere. In people who move from East to West or from West to East (for example, from Vladivostok to Moscow or vice versa) the body temperature varies with the time of day in the new place (Fig. 153) and, consequently, alters compared with the temperature curve in the former place of residence (when it is 4 o'clock in the morning in Vladivostok, i.e., the time of the lowest body temperature, it is 11 o'clock in Moscow, i.e., the time when the body temperature approaches its highest). The diurnal curve of body temperature is determined by the physical factors of the external environment for animals and, mainly, by social factors for man, particularly by the rhythm of the surrounding life which dies down at night.

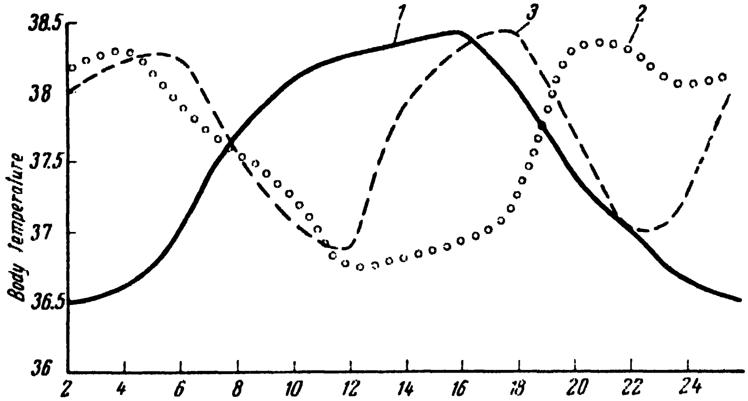

Fig. 154. Distortion of 24-hour curve of body temperature in simians under different feeding and lighting regimes (after O. Shcherbakova). 1—standard, 2—with lighting at night and black-out in daytime, 3—diphasic rhythm.

Diurnal periodical variations are also observed in a number of other physiological functions. Thus, for example, the respiratory rate, the composition of the alveolar air, the pulse rate, the rate of metabolism, the blood pressure, the value of diuresis, the sugar concentration in the blood, etc., are all subject to similar diurnal changes. All these diurnally observed variations are due to the periodical changes in the central nervous system (probably the hypothalamic region and the cortex) which reflect the regime of the bodily activity under the influence of the external environment.

Experimental studies of the diurnal rhythm of the body temperature and other physiological functions, made on simians, have shown that with distortions of the mode of life, i.e., with changes in the food and lighting regime, the temperature curve also completely changes (Fig. 154). Moreover, by lighting the room in which a simian lives twice a day for six hours each and by darkening it for as long a time it has been possible experimentally to create a diphasic day with each phase lasting 12 hours.

The diurnal rhythm is, thus, not an inborn property of the organism, but is developed in the process of individual life. It requires from 5 to 8 days to extinguish or alter the established rhythm. A new conditioned reflex in response to time is, apparently, formed in this case, i.e., it is developed in response to a new cycle of metabolic processes in the organism, changing the organism's total behaviour in a very definite sequence (O. Shcherbakova).

It has not been possible to produce these alterations in the diurnal periodicity of the physiological processes of man under artificial laboratory conditions. These distortions are possible, as before stated, when travelling from East to West or from West to East because they are due to changes in the entire mode of life. It should be noted that night work, even when done for a long period of time (years) does not always alter the diurnal rhythm in man because the diurnal rhythm of the surroundings (social) does not change. That is why in a change of residence (in relation to longitude) the diurnal rhythm alters much faster than in an individual change of work and rest, of sleeping and waking hours.

Muscular activity may markedly raise the human body temperature. In this case a veritable "fever" reaching 38° C and higher is observed; after cessation of work the temperature rapidly returns to normal. The rise in temperature during work cannot explain the diurnal variations in the body temperature because the latter occur even in strictly bedridden people and form a sort of time "measure" for the central nervous system, a "measure" based on the conditioned-reflex mechanisms.

The temperature of the body varies most with the extremes of external temperatures.

A small rise in body temperature (within the limit of 1°) may be observed in man and animals at a low external temperature. Only as a result of considerable and prolonged cooling does the temperature of the body begin to drop. The rise in body temperature during moderate cooling is explained by the fact that the heat production exceeds even the physical loss of heat which increases as the temperature drops. A slight drop in body temperature can similarly be observed under the influence of moderate heating.

The foregoing explains the fact that no differences in the human body temperature under various climatic conditions have been found as yet. The greatest variations in body temperature under thermal influences of the external environment are normally always fully compensated by the changes in heat production and heat loss which constitute the phenomena of thermoregulation.

The limits of external temperature within which a constant body temperature can be maintained are entirely different for man and animals. For modern man it all comes down in most cases to a slight variation (several degrees) in the "under-the-clothes" climate. As to animals, especially under arctic conditions, cases are known in which a constant body temperature of 40° C is maintained at an environmental temperature of —60° C. The difference between the external and internal temperature of the polar fox, for example, may reach 100° C. Of enormous importance here are the peculiarities of the animal's integuments (hair and the subcutaneous layer of fat) which play the same part in the struggle against body cooling as warm clothes do for man (diminution of heat loss).

The ability of an organism to adapt itself to high external temperatures is much more limited. Most animals (including those that live in the tropics) cannot stay in a temperature above 45 to 50° for any length of time. In man and certain simians (with well-developed perspiration) the body temperature is maintained at a constant level even at very high external temperatures (up to 45° C) depending on the relative humidity of the air. Man can also endure unusually high temperatures, up to 100° C and higher, for very brief periods of time (a few minutes). In these cases, however, the body temperature shows a considerable rise.

Chemical Heat Regulation

Chemical heat regulation implies all the physiological processes which condition the changes in metabolism and in heat production in the human or animal body. Chemical heat regulation manifests itself in increased metabolism under the influence of low environmental temperature. In this case the increased heat production protects the body against cooling. Contrariwise, under the action of high environmental temperatures metabolism decreases which is one of the ways of fighting overheating. Fig. 155 shows changes in human metabolism at different external temperatures. Comparative physiological studies show that under normal conditions chemical heat regulation in man is less pronounced than in animals. This phenomenon is due to the well-developed regulation of the lumens of the cutaneous vessels in man and the conditions of his existence (clothes, dwelling) which reduce the loss of heat. An increase in metabolism during cooling can be observed in man and animals at complete muscular rest. Further cooling leads to a greater increase in metabolism because of the appearance of shivering. *Muscular movements* may be of even greater importance. Special studies have shown that simians perform a greater number of jumps in winter (vertical, in particular) than in summer; these movements ensure intensified heat production under conditions of cooling.

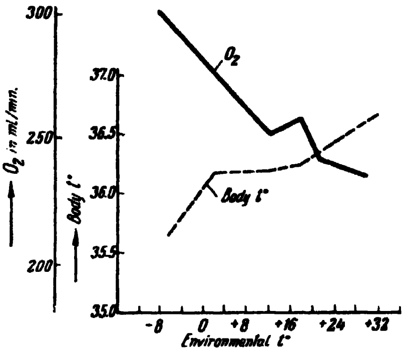

Fig. 155. Chemical heat regulation in man.

Changes in oxygen consumption and in body temperature at different environmental temperatures shown under abscissa.

It is clear that metabolic changes in the skeletal muscles play the principal part in the chemical heat regulation. As the external temperature drops a considerable part of surplus heat can also be produced in the liver. Denervation of the liver in animals reduces the intensity of their chemical heat regulation.

During cooling the changes in the metabolism of the muscles occur as a result of shivering and of regulation by the nervous system of the tissue metabolism, changes which do not have to involve muscular contractions. By completely eliminating muscular movements in animals with the aid of curare and by maintaining life by artificial respiration it is still possible to observe an increase in metabolism during cooling. This phenomenon, known as "chemical muscle tone," reflects the direct trophic influences of the nervous system on the metabolism in the skeletal musculature.

The same has been confirmed by experiments studying the metabolism in an isolated extremity of the dog under conditions in which only a neural connection with the body was maintained. These experiments (Freund and

Jansen) have shown that metabolism in such an extremity fed by defibrinated blood increases simultaneously with the increase in the metabolism of the cooled organism. Cutting the main nerve trunks, but leaving the vessels intact does not destroy the neural connections with the body. It has been found that chemical heat regulation can be effected through the nerve fibres running in the adventitia of the large vessels. Destruction of these nerve fibres by painting the vessels with carbolic acid terminates the effect of metabolic regulation.

The nervous influences which regulate the intensity of heat production (metabolism) in accordance with the changes in the environmental temperature, i.e., the influences which ensure chemical heat regulation, are conducted to the musculature and, probably, to the liver along sympathetic nerve fibres.

L. Orbeli and A. Tonkikh have shown that after removing the sympathetic nervous system stimulation (puncture) in the region of the tuber cinereum does not cause any increase in metabolism or in body temperature, whereas normally this puncture raises the body temperature for several days. Other experiments have confirmed the importance of the sympathetic nervous system as a conducting apparatus propagating impulses, which determine the changes in metabolism from the central nervous system. However, heat is chemically regulated not only by direct influences of nerve impulses on the muscle metabolism and the liver,* but also through the action of hormones. Variations in the hormone concentration in the blood connected with the changes in environmental temperature also depend on the nervous system.

The thyroid gland plays an important part in chemical regulation of heat; this function is also regulated by the central nervous system. With the removal of the thyroid chemical heat regulation sharply decreases; its function also diminishes in animals during winter hibernation. After extirpation of the spinal cord below the first thoracic segment some heat regulation is retained, but it disappears after severance of the nerve fibres which innervate the thyroid gland and run to it from the first thoracic segment of the spinal cord through the cervical sympathetic ganglion.

The adrenals also come into play in the regulation of heat.

Physical Regulation of Heat and Channels of Heat Loss

Physical regulation of heat implies the sum total of the physiological processes which lead to an increase or decrease in the loss of heat by the body. Heat may be lost into the environment in three ways: by convection, radiation and evaporation. Heat is lost by convection when the temperature of the air or of the surrounding objects (with which the surface of the body comes in direct contact) is lower than that of the skin. Heat loss by radiation may occur when the temperature of the air corresponds to that of the skin, but the temperature of the surrounding objects located at some distance from the animal or man is lower. The loss of heat in a room with warm air but with cold walls is a typical example of heat loss by radiation. Heat loss by evaporation is connected with the output of heat for the evaporation of sweat by the surface of the skin and of water—by the surface of the respiratory passages and the alveoli.

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* Of course, the metabolic changes in the other organs also play a part in the chemical regulation of heat, though a quantitatively small part.

Even when no perspiration is visible (at a temperature of 15 to 20° C) a certain amount of water (about 0.4 to 0.6 litres per day) evaporates through the skin (*perspiratio insensibilis*). Since the expired air is always practically fully saturated (95 to 98 per cent) with water vapours, which have the temperature of the body, and the inspired air is usually only 50 to 80 per cent saturated with them, 0.3 to 0.4 litres of water a day is also evaporated with the expired air. Thus, even at moderate temperatures man evaporates 0.7 to 1 litre of liquid per day which corresponds to a heat loss of 400 to 600 large calories and constitutes 20 to 30 per cent of the total heat loss. Much more heat is lost by evaporation at high environmental temperatures.

Heat loss may widely vary with the functions of the special physiological mechanisms which regulate it, i.e., with physical heat regulation. These mechanisms include the reaction of the cutaneous vessels, perspiration, the reaction of the smooth muscle fibres of the skin and the changes in the position of the body.

When environmental temperature is below 10° C, 70 to 80 per cent of the heat is lost by convection and radiation. In this case vascular reaction plays the principal part in the regulation of heat loss. The skin and, especially, the layer of the subcutaneous fatty cellular tissue are very poor heat conductors owing to which heat is very slowly conducted directly from the internal parts to the skin; for practical purposes the value of heat lost by convection is determined by the amount of blood flowing through the vessels of the skin because the blood is noted for its high heat conductivity. The less blood flows through the cutaneous vessels the lower the temperature of the skin and, consequently, the smaller the difference between the temperature of the skin and that of the environment.

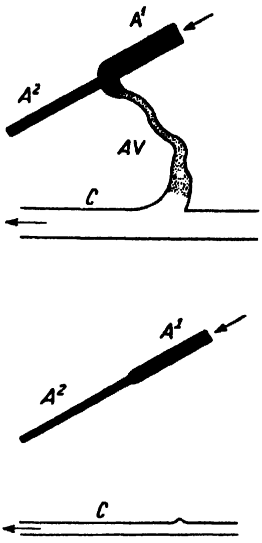

Fig. 156. Reactive contraction of cutaneous arteriovenous anastomosis.

A^1 and A^2—arteries, AV—arteriovenous anastomosis; C—vein. Top—anastomosis open, bottom—anastomosis obliterated.

The most important way of reducing the loss of heat is to reduce the flow of blood to the skin. This is accomplished by a constriction of the arterioles of the subcutaneous vascular plexus (Fig. 156). As the cutaneous vessels become constricted the skin turns pale and the temperature drops. Cooling causes a constriction not only of the cutaneous vessels, but also of the deeper ones, especially in the extremities, which leads to a reduced circulation in these vessels. In this case the blood depots (spleen and liver) receive a good deal of the blood.

Voluntary regulation of heat loss achieved by a choice of clothes depending on the environmental temperature is of extreme importance to man. The fur plays a big part in limiting the heat loss in animals. Heat loss varies with the change of the fur in autumn and spring (moulting); it is made to conform with the temperature of the coming season. During summer and autumn many animals accumulate a lot of fat (this also occurs with aquatic mammals) which also contributes to lowering the heat conductivity of the skin.

A contraction of the smooth muscles of the skin (*mm. arrectores pilorum*) is observed at low temperatures; as a result of this contraction the position of the hair in the fur alters at the same time changing the amount of air in the fur and its heat-protective properties. Man has retained a rudiment of this reaction in the form of "goose flesh" observed in cooling. A similar reaction is also noted in simians.

Changes in the position of the body should also be included in the phenomena of physical heat regulation. At low environmental temperatures some animals curl up in a manner that reduces the total surface of the body exposed to cooling. In some measure this also holds true for man.

Perspiration

The maintenance of a normal body temperature at a high environmental temperature requires a greater loss of heat. This is accomplished by a dilatation of the cutaneous vessels, by a change in the position of the animal's body ("sprawling") and by a change in the pitch of the hair in the fur.

But all these reactions of the body can increase the heat loss only within the limits of environmental temperatures which are below the temperature of the skin. At environmental temperatures above that of the skin heat is lost only by evaporation. Since the body has only two channels for evaporation of liquid—the surface of the skin and the surface of the respiratory passages—the physiological mechanisms for regulating heat loss by evaporation discharge precisely this function. Evaporation from the surface of the human skin increases owing to a change in the function of the sweat glands. Some animals, for example, the horse and the simians, have a similar mechanism.

Man perspires very little at low and moderate temperatures, but his perspiration sharply increases at high temperatures. A very rapid increase in the secretory function of the sweat glands, a "profuse sweating," is characteristic of high temperature. Direct studies of the amount of sweat secreted on the surface of the human skin show that the sweat glands react very strongly to changes in the production of heat.

Very hard muscular work and consumption of hot liquids sharply increase perspiration. Secretion of 5 to 6 litres of sweat a day in hard muscular work is a rather frequent occurrence and sweat is secreted even in freezing weather. Prolonged exposure to high environmental temperature and hard muscular work may cause man to lose 10 to 12 litres of water a day through sweating.

The intensity of perspiration is determined by weighing man in the beginning and at the end of the examination. The loss of weight plus the weight of the water and food consumed minus the voided urine and faeces indicate the value of perspiration.

The sweat glands are innervated by fibres belonging to the sympathetic nervous system; these nerve fibres are axons of cells located in the sympathetic ganglia. The peculiarity in the function of these axons (postganglionic sudoriferous sympathetic nerve fibres) is that adrenalin does not influence the sweat glands; their secretion is stimulated by acetylcholine.

The central efferent mechanisms of perspiration are located segmentally along the entire spinal cord corresponding to the distribution of the neurons from whose axons the sympathetic fibres are formed. Regional disorders of perspiration are, therefore, an important diagnostic symptom of disease of corresponding divisions of the spinal cord.

Role of Respiration in Heat Loss

In a number of animals that have no sweat glands (for example, dogs) heat loss by evaporation is effected through changes in the frequency and depth of respiration, the so-called thermal *polypnoea*. The latter consists in a marked acceleration of breathing (120 to 600 respirations per minute). In polypnoea the respiratory movements are shallow, the mouth is open, the tongue hangs out and a greater amount of thin saliva is secreted. All this leads to evaporation of considerable amounts of liquid from the surface of the oral cavity and the upper respiratory passages and to a considerable cooling of the body. If the dog is muzzled even a brief stay in the sun leads to a sharp increase in its body temperature and death.*

Polypnoea (like the other physiological mechanisms of heat regulation) is an extraordinarily fine mechanism for balancing the temperature of the body's internal and external environment. A more or less appreciable rise in the dog's body temperature is preceded by polypnoea. In dogs, particularly in long-haired animals, heating is unusually rapidly followed by polypnoea. It is easily inhibited by various external stimuli (strong sound, light, etc.). Conditioned-reflex polypnoea can be easily produced in dogs. In pups polypnoea appears on the 12th day after birth, i.e., towards the beginning of conditioned-reflex activity which unites the regulation of movements and vegetative functions.

With the destruction of the dog's midbrain thermal polypnoea disappears.

Role of Vascular Reactions in Heat Regulation

Vascular reactions to thermal influences are conditioned by complex reflex regulation including a combination of unconditioned and conditioned reflexes. After extirpation of the cortex, with the midbrain left intact, the superficial vessels in homoiothermal animals show a dilatation in heating and a constriction in cooling (local vascular reactions in the heated skin have been observed even after denervation of the cutaneous vessels and the skin in general). However, normal vascular reactions to temperature influences always depend on the fine cortical regulation. Numerous studies have established the possibility of developing conditioned reflexes for dilatation and constriction of vessels under the influence of various stimuli which signal the action of cold or heat as unconditioned stimuli (in these cases heat and cold were applied directly to the skin, or the walls of the stomach were stimulated with cold). A combination of these stimuli with a sound or light signal leads to the development of conditioned reflexes which cause identical changes in the lumens of the vessels. Similar effects are caused by verbal stimuli. For example, the effect of vascular dilatation can be observed in a person to whom the words "I am applying heat" are addressed while his plethysmogram is being recorded. The vessels become dilated even when these words are accompanied by the action of a cold stimulus. In this case a verbal stimulus proves more efficient than the direct action of the cold on the receptors of the skin. The subcortical mechanism of thermoregulation is, consequently, under the control of the cerebral cortex.

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* Thermal polypnoea is sometimes incorrectly referred to as thermal dyspnoea. Polypnoea has nothing in common with the phenomena of dyspnoea because it is always accompanied by a decrease in the content of carbon dioxide and an increase in the concentration of oxygen in the blood and in the alveolar air. The onset of dyspnoea inhibits the reaction of polypnoea.

The vascular mechanism of heat regulation is revealed by plethysmography and by studies of the temperature of the skin. The changes in the skin temperature of man and animals caused by application of a cooled or heated body or by exposure to wind are largely due to dilatation or constriction of the cutaneous vessels. Variations in the temperature of the skin reveal in large measure the condition of the superficial vessels, mainly those of the skin.

Central Nervous Mechanism of Heat Regulation

The heat and cold receptor endings in the skin (Chapter 67) in the mucosa of the respiratory passages and in the internal organs (digestive tract) form the receptor apparatus the stimulation of which reflexly causes a reaction of thermoregulation. The direct action of the blood temperature on the nerve centres is only of minor importance because the reflex changes in thermoregulation come into play before there is any alteration in the temperature of the blood. The warming of the blood may exert an appreciable influence only in certain pathological conditions which markedly reduce the sensitivity of the complex-reflex mechanism of thermoregulation (for example, in anaesthesia, in cerebro-cortical disorders and in fever).

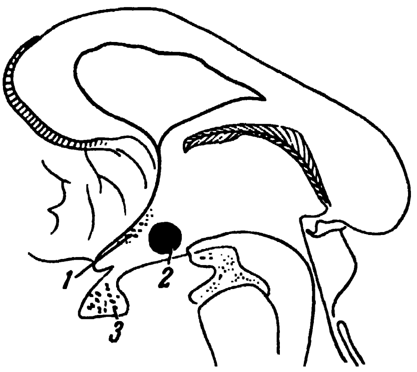

Fig. 157. Diagram of central nervous mechanisms of heat regulation.

1 tuber cinereum; 2—corpora mammillaria; 3—hypophysis.

The diencephalon is the main seat of the lower centres of heat regulation. The lower central neural structures which regulate all the complex processes connected with heat exchange are located in the tuber cinereum, in the floor and the walls of the third ventricle (Fig. 157). Destruction of the tuber cinereum or its disconnection from the lower divisions of the brain give rise to stable poikilothermy, and the animal dies with symptoms of lowering body temperature even when the temperature of the environment remains normal. The main centres of heat regulation are located in the hypothalamic region of the brain which is the lower division of the central apparatus of chemical thermoregulation. Stimulation of this region with induction current causes a rise in body temperature. A lowering of the temperature of the blood which flows to the region of the midbrain produces a similar effect.

Indications have lately appeared that it is possible to maintain an animal's body temperature within certain limits even after severing the brain stem which, thus, separates the body from the aforesaid centres of thermoregulation. Some compensation, apparently, occurs because of the reflex arcs closing in divisions of the central nervous system below the diencephalon (N. Popov). However, the range of adjustment to various temperatures of the external environment and the physiological significance of these phenomena can in no way compare with the powerful processes of thermoregulation brought into play by the higher divisions of the central nervous system.

In addition to the tuber cinereum, the medulla oblongata and subcortical structures heat regulation is, undoubtedly, influenced by the neural elements of the so-called *corpus striatum* (Chapter 59). According to the data of the eighties of last century, which were, incidentally, the first to show the results of the studies of localizing the heat regulation mechanisms, a puncture into the corpus striatum (so-called heat puncture) produced a rise in temperature which lasted many days (Ch. Richet et al.). With the extirpation of the tuber cinereum the effect disappears. The statement of this fact exhausts the information on the role of the corpus striatum in thermoregulation.

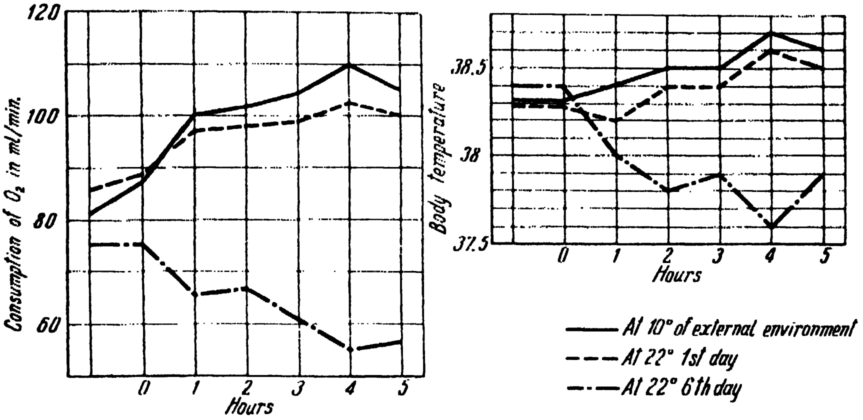

Fig. 158. Conditioned-reflex changes in chemical heat regulation in the dog (after R. Olnyanskaya and A. Slonim) (explanation in text).

With a normally functioning central nervous system the midbrain and the corpus striatum are under the constant influence of the cerebral cortex which initiates the processes of thermoregulation according to the conditions arising during the individual's lifetime.

Studies conducted in the laboratory headed by K. Bykov (A. Slonim et al.) have shown that the conditioned-reflex mechanisms of chemical thermoregulation play a very big part in maintaining the constancy of body temperature and in regulating metabolism. This finds proof, for instance, in the fact that a dog daily brought into a room with a temperature of 12° C and kept there for 4 hours develops a high rate of metabolism under the influence of the low environmental temperature, the rate of metabolism increasing from the first hour to the fourth. After 10 to 12 repetitions of this experiment the dog is brought to the same room, but the room temperature is now maintained at 22° C from the very outset. The dog shows the same high metabolic rate under these conditions as it did at 12° C, the metabolic rate rising from the beginning to the very end of the experiment. By putting the dog daily in the room with a 22° C temperature it is possible to observe a lowering of metabolism which after the same 10 to 12 days is maintained at a low rate from the beginning to the end of the experiment (Fig. 158). In this case we are dealing with a conditioned-reflex reorganization of the chemical heat regulation, a stable reorganization which requires considerable time for its extinction. In experiments conducted in the reverse order, in the absence of conditioned reflexes developed in response to cooling or heating (including the time of day when this takes place) chemical thermoregulation manifests itself very weakly and starts much later than the influence of the temperature.

Similar experiments performed on a number of representatives of mammals and birds have fully confirmed the data obtained on dogs. Cortical regulation of heat and metabolism is, apparently, an important and general physiological law for the higher animals.

Similar facts were established for man both in laboratory investigations and in studies of heat exchange under conditions of customary work. For example, facts testifying to the importance of the conditioned-reflex mechanism of chemical thermoregulation in man were established by studies of railway workers—freight train conductors in winter. As the conductor moved away from the point of departure with its warm room, where he had stayed before leaving, the gaseous exchange sharply increased. On the way back the consumption of oxygen decreased the closer the moment when the conductor would find himself in a warm room. In both cases the conductor was continuously exposed to the same intense cold and none of the physical conditions of heat loss were altered. People who never travelled on an open platform and were never exposed to cold for long periods of time showed a much lower metabolic reaction. During the ride on the brakeman's platform they experienced oppressive sensations of chilling; the conductors did not have these sensations.

The conditions under which the effect of cold is felt and the very work done at this time become signal stimuli for the processes of chemical thermoregulation in man. The latter is particularly closely connected with cortical influences on metabolism.

Thus, the centres of thermoregulation function reflexly when corresponding receptors are stimulated. There are no isolated subcortical reactions of thermoregulation, however, because in the process of individual life all regulation of the heat exchange is subject to the control of the cerebral cortex as a result of the development of numerous extero- and interoceptive conditioned reflexes. The processes of heat regulation, a very important factor in the constant relations between the body and the environment, become highly specific under conditions of rest and multifarious activity. This specificity explains many questions in the adjustment of the body to the thermal conditions of the environment.

Heat Regulation Under Natural Conditions of Existence

The combination of conditioned and unconditioned reflexes, which come into play under the influence of stimuli of the external environment, produces various changes in chemical and physical thermoregulation.

The natural signals concomitant with the heating or cooling of the body all through its life play an especially important part in heat regulation. Thus, a constriction of vessels may be observed by showing a person ice on a hot day; the reaction of polypnoea can be brought about in the dog by solar radiation at a low environmental temperature. This signalization enables the body to react quickly by thermoregulation in response to changes in the external or internal thermal conditions.

These mechanisms undoubtedly play a prominent part in the body's adjustment to heat and cold, which is usually referred to as temperature acclimatization. The complex-reflex mechanisms of heat regulation are also very important in the reaction of the body to complex combinations of cooling or heating stimuli. Thus, for example, the movement of air (wind) exerts a cooling influence on the body (increase in convection) because of a better exchange of the air heated near the surface of the body. If we set warm air in motion that does not physically cool the body it causes a reaction characteristic of cooling, i.e., an increase in metabolism, because under the natural climatic conditions of the central zone a movement of air usually causes an increase in heat loss. In this case the wind is a natural conditioned stimulus, a signal for cooling.

Under conditions in which heat loss by radiation prevails, for example, in a building with metal walls or in one heated by stoves, i.e., in a building with warm air and cold walls, the reaction of thermoregulation (increase in metabolism, constriction of cutaneous vessels) markedly decreases or appears a long time after the beginning of cooling. In these cases the natural signal stimulus--the effect of the cold air on the receptors of the skin and mucous membranes—drops out. This form of cooling, extremely unfavourable to the body, causes a considerable lowering of the body temperature due to the weak and late reaction of thermoregulation. The normal reaction to heat and cold, which equalizes the body temperature with sufficient speed and precision, apparently, comes into play in the body only according to a certain pattern—a combination of stimuli developed in the course of individual life. A breach in this pattern both in heating and cooling reduces the speed and precision of the thermoregulatory reaction and may lead to pathological phenomena. This is also evident from the fact that workers in a refrigerating plant who find themselves in it under uncustomary conditions (in an unusual horizontal position) hardly show the increase in the consumption of oxygen (heat production) at a low temperature that always occurs in the same workers when they are in the same circumstances and at the same temperature, but under customary conditions—in a sitting posture.

Knowledge of the physiological mechanisms which ensure a high degree of the body's resistance to cooling, i.e., inure it to cold, is of considerable practical importance. More or less brief exposures to cold in combination with physical exercises or games are ordinarily used to inure the body to cold. A high degree of resistance to cold may be developed by water procedures—sponging down with cold water, showers, bathing (for example, in autumn) at a continuously lowering temperature in natural reservoirs. A similar effect is produced by continuously lowering the temperature of the air which contacts a large surface of the naked human body. Studies have shown that the process of inuring the body to cold leads to a certain rise in the temperature of the skin, especially of the extremities. An increase in metabolism, more pronounced under the action of a cold stimulus, is observed at the same time. Thus, for example, physical exercises in seasonal clothes, even if performed outdoors during the autumn and winter season, do not increase resistance to cooling. Similarly, too great physical exertion in cold air, which does not produce the sensation of cooling, does not lead to an increased resistance to cold despite the numerous repetitions of the exercises.

Adjustment to high environmental temperatures consists in a decrease in heat production and in perspiration followed by an increase in heat loss by convection (dilatation of the cutaneous vessels). This is accompanied by a decreased consumption of water which is of considerable importance to maintaining the salt composition of the blood frequently unbalanced by abundant perspiration. A certain decrease in the intensity of muscular movements (in animals) must, apparently, also take place.

Thermoregulation during muscular activity reduces the sensitivity of the body to cooling, especially external cooling. Muscular activity and the increased heat production associated with it must be regarded, on the one hand, as an intensive interoceptive heat stimulus which inhibits, probably by way of cortical induction (Chapter 62), the effect of exteroceptive thermal cold stimuli. On the other hand, the introduction of interoceptive thermal stimuli during muscular work (for example, drinking hot water) causes a lowering of the general metabolism, including the energy output for muscular activity. Studies have shown that interoceptive thermal conditioned reflexes continuously inhibit the exteroceptive reflexes, i.e., the increased internal heat production reduces the precision in the regulation of the body temperature under the cooling action of the external environment.

The factors of the external environment connected with the seasons and the diurnal cycle exert a tremendous influence on the processes of thermoregulation. Chemical thermoregulation is more intensive in winter than in summer. Contrariwise, the reaction of the cutaneous vessels (physical thermoregulation) is greater in summer. In the daytime (also under the influence of the rays of the visible part of the spectrum) chemical thermoregulation is more vigorous than at night. Utilization of these factors is of considerable importance in the struggle against chilling under different conditions of human activity.

PART IX

EXCRETORY PROCESSES

The processes of excretion consist in the elimination of compounds which are formed during tissue metabolism and cannot undergo any further changes in the body. The excretion of these compounds, known as the *end products of metabolism*, is the last stage in the metabolic exchange between the body and the external environment.

All metabolites excreted from the body (except gases) are voided in the form of aqueous solutions. Water, therefore, constitutes the bulk of the excreta by weight.

In addition to the compounds which are formed during tissue metabolism and which do not undergo further transformations in the body (end products of metabolism) the latter, as a result of excretory processes, also voids compounds formed by disintegrated cells and the foreign bodies which enter the organism with the food.

The excretory processes play a most important part in maintaining the relative constancy of the body's internal environment without which life is impossible. The higher the phylogenetic development of the organism and the more developed its nervous system the more sensitive it is to variations in the constancy of its internal environment.

Disorders of the excretory processes kill higher animals much faster than do food deficiencies. Whereas complete starvation (but with drinking water necessary for the same excretory processes) results in the death of a human being in only 10 to 20 (sometimes less and sometimes more) days the full cessation of the excretory functions of the kidneys alone causes death in a few days.

The products eliminated from the body are known as *excreta*. They include: a) carbon dioxide eliminated (by terrestrial animals) almost exclusively with the expired air through the lungs; b) end products of protein metabolism, mainly urea, but also uric acid, creatinine and other nitrogenous compounds; c) products of incomplete oxidation of organic substances, for example, lactic acid and acetone bodies; d) inorganic compounds, i.e., salts, a certain amount of which is always excreted by the body (even when they are not consumed with the food); e) foreign bodies which are consumed with the food and which do not take part in metabolism; f) water.

All of the substances excreted by the body (except CO_2) pass through the kidneys; a small amount of them is also eliminated with the sweat through the skin and with the faeces through the intestines.

CHAPTER 36

EXCRETORY FUNCTION OF KIDNEYS

The urine is formed in the kidneys and is eliminated from the body through the urinary channels. At least 98 per cent of the urine is water in which all the end products of nitrogenous metabolism (urea, uric acid, creatinine and certain other products of protein metabolism in the body, small amounts of which are contained in the urine) and the products of protein putrefaction absorbed from the intestines, are dissolved. The products of incomplete oxidation of proteins, fats and carbohydrates (lactic, beta-oxybutyric and acetoacetic acids, acetone, etc.) are also eliminated with the urine. The excretion of these substances considerably increases during oxygen deficiencies (for example, at high altitudes and in extremely hard muscular work) and in disorders of normal carbohydrate metabolism (in diabetes and in a high fat diet).

Structure of Kidneys

Microscopic studies show that the kidneys contain an enormous number of structures which do not communicate with each other and stand apart morphologically; these structures are known as *nephrons* (Fig. 159 and 160). The number of nephrons in both kidneys may reach 2,000,000.

The initial division of each nephron, the so-called *Shumlyansky's corpuscle* contains a microscopic cavity. A long and narrow renal tubule, in which several divisions are also distinguished, arises from this cavity. The nephrons do not communicate with each other all through their length until the renal tubule enters the collecting tubule.

The remarkable Russian microscopist A. Shumlyansky was the first to establish in 1783 that each renal tubule arises from a microscopic cavity into which a tuft of capillaries, the malpighian glomerulus, hangs down. Shumlyansky, thus, discovered the characteristic feature of the nephrons—the continuity of each nephron, which includes the cavity of Shumlyansky's corpuscle (Shumlyansky's cavity) with a continuous tubule arising from this cavity and not communicating with the neighbouring tubules. Eighty years after Shumlyansky the English investigator Bowman confirmed all these data and added an indication of the existence of a very thin membrane which covers the capillaries hanging down into Shumlyansky's cavity (having no oil-immersion objective-glass Shumlyansky could not have seen this membrane).

The structure of Shumlyansky's corpuscle is shown in Fig. 159. It is an almost spherical hollow formation with a tuft of capillaries—the *malpighian glomerulus*—formed by a number (up to 50) of capillary loops, pressed into it. These loops are formed from the arteriole—the *vas afferens* (see below), which divides into capillaries directly it enters Shumlyansky's corpuscle; then all the loops of the capillaries of the malpighian glomerulus anastomose to form the *vas efferens* which begins at the very exit from Shumlyansky's corpuscle. The latter, therefore, resembles a spherical goblet whose very narrow neck is filled with the afferent (entering the corpuscle) and efferent (leaving the corpuscle) blood vessels, while the cavity is nearly completely filled with the loops of the capillaries of the malpighian glomerulus; each of these loops arises from an afferent and empties into an efferent vessel. Each loop is invested with a very thin (1 to 3 μ thick) membrane (Bowman's capsule). This capsule is the continuation of the layer of cells involuting into Shumlyansky's corpuscle and forming its outer wall. The blood in each loop of the glomerular capillaries is, thus, separated from the cavity of Shumlyansky's corpuscle by one layer of cells of the capillary endothelium and one layer of very thin cells which form Bowman's capsule.

The renal tubule begins from the cavity of Shumlyansky's corpuscle (Fig. 160). It consists of three divisions: the proximal convoluted tubule, the loop of Henle and the distal convoluted tubule. The *proximal convoluted tubule* begins directly from the cavity of Shumlyansky's corpuscle and makes two or three bends in the cortical substance of the kidney. Its walls are formed by one layer of cuboid epithelial cells whose surface, facing the lumen of the tubule, has a so-called "brush border"—numerous very thin threads protruding into the cavity of the tubule. This makes for a resemblance between the epithelium of the proximal convoluted tubule and the absorbing epithelium of the small intestine. The diameter of the proximal tubule is about 50μ (0.05 mm.) and its length—about 15 mm.

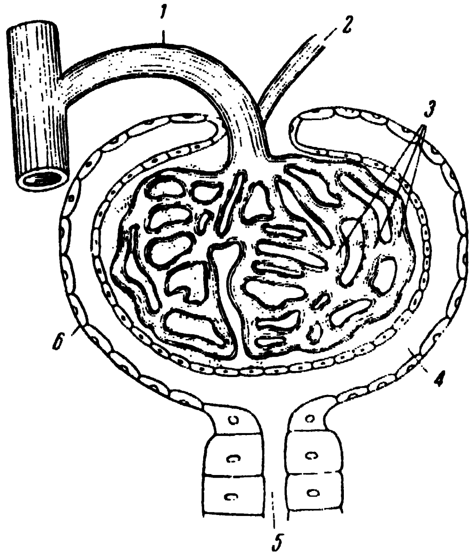

Fig. 159. Diagram of structure of Shumlyansky's corpuscle.

1—vas afferens; *2*—vas efferens; *3*—capillaries of glomerulus; *4*—cavity of capsule of Shumlyansky's corpuscle delimited by capsule of Bowman; *5*—convoluted tubule; *6*—capsule.

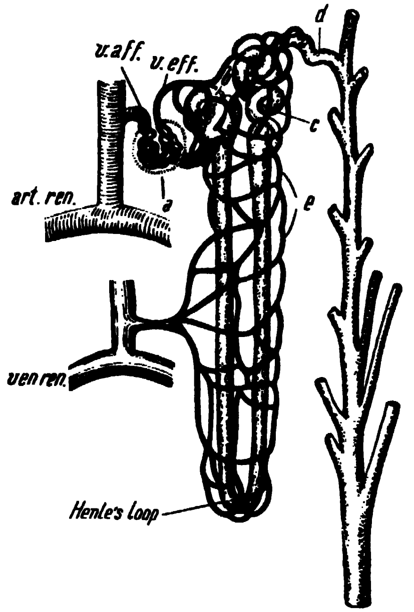

Fig. 160. Diagram of nephron structure.

a—malpighian corpuscle with glomerulus; *b* and *c*—proximal and distal convoluted tubules; *d*—collecting tubules; *e*—capillaries of convoluted tubules; *v. aff.*—vas afferens; *v. eff.*—vas efferens.

The distal tubule passes into the *loop of Henle*, a U-shaped tube running into the medulla of the kidney and returning thence to the renal cortex. The descending limb of Henle's loop, which begins from the proximal convoluted tubule, is much thinner (15 to 20 μ) than the ascending limb which returns to the cortical part. This is the so-called ***thin segment*** of Henle's loop found only in the kidneys of mammals. Henle's loop passes into the ***distal convoluted tubule*** whose cuboid epithelial cells, like those of Henle's loop, have no brush border. This is the terminal division of the nephron.

The total length of the nephron is approximately 35 to 50 mm. With the 2,000,000 nephrons in both kidneys the total length of all the tubules put together is 70 to 100 kilometres, while the total surface of their inner layer equals 5 to 8 $m.^2$ which is 3 to 5 times the surface of the body.

The nephrons end by entering collecting tubules which take no part in the production of urine, but serve only for transporting it to the renal pelvises from which the ureters arise.

Renal blood supply. The blood supply of the kidneys differs from that of all other organs of the body by the fact that the blood flowing into the kidney consecutively passes through two sets of capillaries (Fig. 160): the capillaries of the malpighian glomeruli and those entwining the renal tubules. The capillaries of the malpighian glomerulus are formed from a wide (about 50 μ in diameter) arteriole, a branch of the interlobular arteries which receive their blood from the renal artery. Each arteriole that enters Shumlyansky's corpuscle is called an *afferent vessel* (vas afferens). Upon entering the cavity of Shumlyansky's corpuscle the afferent vessel immediately branches out to form the loops of the capillaries of the malpighian glomerulus. The blood pressure in these capillaries is higher than in any other capillaries in the body reaching 60 to 70 per cent of that in the aorta, i.e., 70 to 90 mm. Hg. This is due to the fact that the afferent vessel is wider and shorter than the arterioles in all the other parts of the body. In flowing through this vessel the blood, therefore, spends little energy on overcoming friction.

Just before leaving Shumlyansky's corpuscle the capillaries of the glomerulus immediately anastomose again into one so-called *efferent vessel* (vas efferens), which because of its structure belongs to arterioles rather than veins. The efferent vessel branches out again as a result of which a second set of renal capillaries is formed; these capillaries entwine all the divisions of the tubular system. Thus, the tubules are bathed by the blood which has already gone through the capillaries of the glomerulus (only a small part of the capillaries which entwine the tubules may arise from arteries that take no part in forming the glomerular capillaries). The blood pressure in the capillaries of the tubules is not high (20 to 40 mm. Hg) since the blood that enters them has overcome the resistance of the glomerular capillaries and the thin efferent vessel.

About 15 to 20 per cent of the total blood pumped by the heart into the aorta circulates through the kidneys; in man this constitutes 1 to 1.2 litres of blood per minute. During muscular work the vessels of the kidneys become constricted and somewhat less blood (10 to 20 per cent) can flow through them than at rest. Much less blood is supplied to the kidneys when adrenalin enters the blood and after considerable haemorrhages.

The regulation of renal circulation is noted for certain peculiarities. In changes of the external temperature the blood supply to the extremities and to the abdominal organs diminishes while the amount of blood flowing through the kidneys usually remains invariable. The renal vessels do not become constricted even when there is a reflex constriction of the vessels of all the other organs of the abdominal cavity in response to a rise in the blood pressure in the region of the receptors of the aorta and the division of the carotid arteries. A novocain block of the nerves running to the kidneys and spinal anaesthesia hardly cause any dilatation of the renal vessels. This means that the tonic tension of the smooth musculature of the renal vessels is usually low. Constriction of the renal vessels due to contractions of their smooth muscles apparently takes place only under special circumstances (for example, muscular work) and is not constant.

Renal nerves. The kidneys are supplied by nerve fibres travelling with the large and small splanchnic nerves and, possibly, with the vagus. The nerve fibres enter the kidneys together with the blood vessels mainly through the hili. These nerve fibres include many afferent fibres which run from receptors located in the kidneys. The efferent fibres running to the kidneys end in the smooth muscles of the renal vessels (both the *vas afferens* and *vas efferens*). Smirnov found (1901) that there were nerves which directly innervated the cells of the tubular epithelium; these are very fine nerve fibres that entwine the epithelial cells and form endings on them resembling the nerve endings in the epithelial cells of certain digestive glands.

Among the afferent fibres running from the kidneys there are some that carry impulses from the receptors to the centre; stimulation of these receptors produces a sensation of pain. These receptors are located mainly in the renal capsule in the beginning of the ureter owing to which the distention of the capsule, for example, when the ureter is blocked by a calculus, causes severe pain.

Differences Between Composition of Urine and that of Blood Plasma

Urine is formed from the blood plasma. The kidney does not produce the constituents of the urine (except ammonia and hippuric acid) and the latter contains only the compounds transported to the kidneys by the blood. Nevertheless, the composition of the urine differs essentially from that of the blood plasma.

The plasma contains about 7 to 8 per cent proteins, while the urine in a normal state is practically free of protein.

The plasma always contains about 0.1 per cent sugar (glucose); in the urine there is no sugar if the concentration of it in the blood does not exceed about 0.17 to 0.20 per cent.

The content of urea in the plasma does not exceed 0.05 per cent; in the urine it may reach 4 per cent.

The osmotic pressure of all compounds dissolved in the plasma corresponds to approximately 7.5 atmospheres; that of the human urine may reach 22 atmospheres. At the same time, if very large amounts of urine are formed, its osmotic pressure may drop below that in the blood plasma.

The pH of the plasma is normally 7.4, while the concentration of the hydrogen ions in the urine varies very greatly, frequently dropping to 5 and even to 4.7, and sometimes rising to 8.

The composition of the blood plasma is constant, while that of the urine widely varies with the nature of the metabolism and of the food and the amount of water consumed.

The following shows the percentages of various substances in the urine and in the blood plasma:

	In the plasma	In the urine
Water	90	at least 98
Proteins	7-9	none
Sugar	0.1	none
Urea	0.03	0.8-3.5
Salts	0.9	0.8-1.8

Consequently, the kidneys produce urine by subjecting the blood plasma, which circulates through them, to a number of changes. Having to explain the processes as a result of which the plasma of the blood was changed into urine by the kidneys, physiologists offered various theories of urine production; they were all based on the characteristic features in the structure of the kidneys and ascribed different functions to the initial part of the nephrons, i.e., Shumlyansky's corpuscles, on the one hand, and to the renal tubules, on the other.

Some aspects of urine production have now been definitely established owing to the development of the methods of microphysiological research. The micromanipulator enabled Richards and other investigators to collect the minutest amounts (about 0.001 ml.) of fluid from different portions of an *individual nephron*, while the achievements in microchemistry have made it possible to subject these minute amounts of fluid to a precise quantitative analysis. This helped to determine the composition of the so-called primary urine, i.e., the fluid found in the initial part of the nephron, in the cavity of Shumlyansky's corpuscle, and the changes in this fluid as it passes through the tubules and is transformed into the "final" urine which runs from the collecting tubules through the ureters into the urinary bladder.

Glomerular Filtration

One of the characteristic features of the initial part of the nephrons, i.e., Shumlyansky's corpuscles, is that the cavity of each of them contains up to 50 loops of capillaries *in which the blood flows under a much higher pressure than in all the other capillaries of the body*. In the middle of last century this led Bowman and later Ludwig to the assumption that there was a *filtration* of the blood plasma from the capillaries into the microscopic cavity of Shumlyansky's corpuscle. The endothelium of the capillaries and the very fine membrane of Bowman's capsule that invests them act as a filter that does not let the blood corpuscles or large protein particles through. Filtering through the endothelium of the capillaries and Bowman's membrane by force of the blood pressure the plasma frees itself of the blood corpuscles and the proteins dissolved in the plasma.

The correctness of this hypothesis was proved when scientists succeeded in penetrating into the cavity of Shumlyansky's corpuscle with a microscopic needle and by compressing the proximal tubule (to avoid drawing in any of its fluid) were able to collect for the subsequent microchemical analysis some primary urine which fills the microscopic cavity of the initial division of the nephron. It has thus been established that in Amphibia and mammals alike the *fluid in the cavity of Shumlyansky's corpuscle contains all the substances found in the plasma with the exception of colloids and that the concentration of all compounds found in the fluid of the initial division of the nephrons corresponds to their concentration in the plasma of the blood.* Sugar, salts, urea, amino acids, in general, all the compounds of a relatively light weight usually contained in the plasma (or artificially introduced into the blood) are found in the primary urine in the same concentration.

The similar composition of the blood plasma and the primary urine found in the cavity of Shumlyansky's corpuscle is explained by the fact that the primary urine is a filtrate of the blood plasma. Since the blood in this case frees itself not only of the blood corpuscles suspended in it, but also of the colloid substances found in it, this filtration is frequently designated as *ultrafiltration* (the blood plasma freed of proteins is, correspondingly, referred to as an *ultrafiltrate*).

Thus, the first stage in the production of urine is the filtration of the protein-free ultrafiltrate of the blood plasma from the glomerular capillaries into the cavity of Shumlyansky's corpuscle. This ultrafiltrate may be called the *primary urine* or the *glomerular filtrate* or the *protein-free filtrate of the blood plasma.*

Gelatin introduced into the blood (molecular weight about 35,000) and haemoglobin (molecular weight about 68,000) may pass from the blood plasma into the glomerular filtrate. The wall of the epithelium is normally impermeable to proteins with a molecular weight exceeding 70,000 (incidentally, the molecular weight is hardly the only determining factor in this case). In diseased capillaries (for example, in nephritis) the walls of the capillaries become permeable to proteins with a greater molecular weight. Under these circumstances the proteins of the plasma, especially albumins with a molecular weight lower than that of globulins, pass into the cavities of the nephrons. Protein is found in the urine as a result. Negligible amounts of proteins are also found in the urine excreted in normal renal function.

Role of blood pressure and of oncotic pressure of colloids in glomerular filtration. Whether filtration takes place in a chemical laboratory or in the body it requires a force to press the liquid through the filter. In the glomerular capillaries this force is the pressure of the blood upon the walls of the capillaries. This pressure of the blood on the walls of the vessels is often designated as hydrostatic pressure. In the glomerular capillaries the blood pressure is 70 to 90 mm. Hg, and varies with the arterial blood pressure.

The pressure of the blood on the walls of the glomerular capillaries is the force that squeezes the ultrafiltrate of the plasma into the cavity of Shumlyansky's corpuscle. This force is opposed by the force of the oncotic pressure of the colloids of the plasma which *draws the water from the cavity of Shumlyansky's corpuscle back into the blood.* It was pointed out earlier that if two solutions are separated by a semipermeable membrane the water from the solution with the lower osmotic pressure passes into the solution with the higher osmotic pressure. All the substances which permeate from the plasma of the blood through the glomerular capillaries into the cavity of the initial division of the nephron (salts, sugar, urea, etc.) have the same concentration in the primary urine and in the blood plasma and, therefore, an equal osmotic pressure. But the colloids (almost exclusively proteins) do not pass into the primary urine. This is why the osmotic pressure of the plasma exceeds that of the primary urine by the value of the osmotic pressure of the colloids of the plasma, i.e., by the value of the oncotic pressure (oncotic pressure is the osmotic pressure of the non-diffusible colloids). Compared with the total osmotic pressure of the plasma this oncotic pressure is low, constituting about 30 mm. Hg out of the 5,500 to 6,000 mm. of the total osmotic pressure of the plasma. Nevertheless, the oncotic pressure of the proteins is a *surplus* osmotic pressure acting *only* from the blood stream. In relation to the primary urine the blood plasma is, therefore, a hypertonic solution with the proteins of the plasma drawing the water from the cavity of Shumlyansky's corpuscle back into the blood with a force equal to the osmotic (oncotic) pressure they produce. It follows that the pressure under which filtration is effected, the so-called *filtration pressure* (FP) corresponds to the difference between the lateral pressure of the blood on the walls of the capillaries (CP) and the oncotic pressure of the proteins of the plasma (OP). We must add to the latter the so-called intrarenal pressure (see below). By designating the latter RP we have: FP = CP — (OP + RP). The higher the filtration pressure, everything else being equal, the more vigorous the filtration; the lower the filtration pressure the weaker the filtration.

Factors affecting value of filtration. Numerous experiments (A. Ustimovich et al.) have shown that production of urine ceases if the arterial blood pressure drops to 40 or 50 mm. Hg. The blood pressure in the glomerular capillaries is always lower than in the arteries; when the latter drops to 40 or 50 mm. Hg the pressure in the glomerular capillaries lowers to the level of the oncotic pressure of the proteins in the plasma; under these circumstances the filtration pressure goes down to zero and the production of primary urine becomes impossible. If we introduce a large amount of Ringer's solution into the blood when urine production ceases or sharply diminishes, i.e., if we reduce the concentration (and, consequently, the oncotic pressure) of the proteins in the plasma, the production of urine increases. This is due to the fact that a drop in the oncotic pressure leads to a rise in filtration pressure.

Glomerular filtration is also influenced by the diameter of the lumens of the efferent and afferent vessels since this affects the blood pressure in the glomerular capillaries. Glomerular filtration increases with the constriction of the efferent vessels (*vas efferens*) of the kidneys, because in this case the flow of blood in the glomerular capillaries and in the afferent vessel slows down and the blood pressure in the glomerular capillaries increases approaching that in the arteries (this is due to the fact that the slower the blood flows through the vessels the less energy it spends on overcoming friction). Contrariwise, constriction of the afferent vessels (*vas afferens*) results in lowered pressure in the glomerular capillaries because the blood spends more energy on overcoming friction before it reaches the capillaries. In the first case glomerular filtration increases, in the second case it diminishes.

The lumens of the afferent and efferent vessels vary with the impulses transmitted to the smooth muscles of the vessels along the sympathetic nerve fibres. The vasomotor nervous influences, thus, affect glomerular filtration. It is clear that the latter is also affected by changes in blood pressure. For example, a rise in general arterial blood pressure leads to greater glomerular filtration if only there is no increase in the concentration of proteins in the plasma and no constriction of the afferent vessels of the kidney.

Significance of intrarenal pressure. In addition to the oncotic pressure of the plasma the blood pressure on the walls of the glomerular capillaries is also counteracted by a pressure existing within the kidneys. This intrarenal pressure is due to the turgor of the renal cells which is responsible for the resistance to the flow of urine along the convoluted and collecting tubules. This factor leads to a rise in the intrarenal pressure because the kidneys are invested in an inelastic renal capsule. Due to the inflexibility of this capsule no obstacle to the flow of urine essentially increases the volume of the kidney, but mainly raises intrarenal pressure. Intrarenal pressure, however, is not high—about 3 to 7 mm. Hg. It increases considerably with resistance to the flow of urine, for example, with calculi passing through the ureters. Under these circumstances urine production is likely to cease due to the drop in filtration pressure caused by the increase in intrarenal pressure, i.e., owing to the increase in the RP factor in the expression FP = CP — (OP + RP). In these cases an incision of the renal capsule may restore the production of urine.

By pumping liquid into the ureter against the flow of urine A. Ustimovich measured the value of intrarenal pressure at which the production of urine ceases. It appears that this occurs when the pressure in the ureters rises to 30 or 40 mm. Hg, i.e., the value which, added to the oncotic pressure, corresponds to the blood pressure in the glomerular capillaries. This reaffirms the significance of filtration pressure as a factor determining the production of primary urine.

Glomerular filtration does not have to liberate any energy in the renal tissue because the work required for filtration is done by the energy imparted to the blood by the heart and expressed in the value of the blood pressure. This is why a cessation or diminution of the oxidative exchange in the kidney caused by cyanide poisoning or cooling does not decrease filtration of the plasma from the capillaries into the cavity of Shumlyansky's corpuscle.

Inadequacy of concept of glomerular filtration. The facts known to us today warrant the characterization of the first phase of urine production, i.e., the processes in Shumlyansky's corpuscle, as an ultrafiltration of the plasma from the glomerular capillaries into the cavity of the initial division of the nephron. It seems quite likely, however, that this concept somewhat simplifies the real state of affairs. To compare the wall of the endothelium of the glomerular capillaries and Bowman's capsule with a filter whose properties are determined only by the value of invisible "pores" which do not let through any blood corpuscles or large colloid particles is quite primitive. Though the plasma passes from the capillaries into the cavity of Shumlyansky's corpuscle under the action of filtration pressure, it does not mean that the properties of the given "filter"—the endothelium of the capillaries with an extremely thin capsule in which they are invested—are constant. It is possible that filtration takes place not only through the "pores" between the cells, but also through the very cells of the endothelium. It must, therefore, be assumed that the vital activity of the tissues of Shumlyansky's corpuscle affect their permeability and, consequently, the rate of filtration. Appreciable changes in the properties of these tissues also affect the composition of the glomerular filtrate.

Modern concepts of glomerular filtration as a simple physicochemical process must be considered only relatively valid. In the future, when physiology learns to investigate microprocesses in the tissues under conditions close to normal (which can in no way be said of the conditions of Richards' experiments) we shall probably find mechanisms of fine physiological regulation of glomerular filtration.

Tubular Reabsorption

The composition of the urine excreted from the kidneys differs essentially from that of primary urine (the glomerular filtrate) which is of a nature of a protein-free ultrafiltrate of the blood plasma.

Table 23 shows the average composition of the blood plasma, its glomerular ultrafiltrate (primary urine) and urine (the composition of the latter may greatly vary with the state of the water and salt metabolism and the activity of the entire organism, though the figures in Table 23 may be taken as average and characterizing the urine when relatively small amounts of it are excreted).

What are the physiological mechanisms by which the ultrafiltrate of the plasma (primary urine) acquires in passing through the tubules the composition of the "final" urine excreted from the body? According to the theory, advanced long ago by Ludwig and later developed by Cushny, water, part of the salts, urea and sugar, which enter the initial division of the nephron with the ultrafiltrate of the plasma, are *reabsorbed into the blood* in the renal tubules. When the study of the primary urine, taken directly from the microscopical cavity of Shumlyansky's corpuscle, showed that the composition of the primary urine and that of the protein-free ultrafiltrate of the blood plasma were identical, physiology was given incontestable proof of the existence of reabsorption, at least in relation to sugar, because sugar (glucose) is always found in primary urine and is

Table 23

Average Composition of Blood Plasma, Primary Urine and Final Urine in %
(After Cushny)

	Blood plasma	Primary urine	Final urine
Water	90-92	About 99	98-99
Proteins, fats, glycogen	7-9	Absent	Absent
Glucose	0.1	0.1	Absent
Sodium (in the form of ions)	0.3	0.3	0.4
Chlorine (in the form of ions)	0.37	0.37	0.7
Potassium (in the form of ions)	0.02	0.02	0.15
Sulphate (in the form of ions)	0.002	0.002	0.18
Magnesium (in the form of ions)	0.0025	0.0025	0.006
Urea	0.03	0.03	2.0
Uric acid	0.004	0.004	0.05
Creatinine	0.001	0.001	0.075

usually absent in the final urine excreted from the kidneys. It follows that sugar is undoubtedly reabsorbed into the blood from the tubular urine (we shall thus call the urine flowing along the tubules and changing its composition as a result of the processes occurring in the tubules).

Microphysiological methods have made it possible to collect fluid not only from the cavity of Shumlyansky's corpuscle, but also from different portions of the renal tubules, and to determine its composition and quantity. It has been shown that:

a) all of the sugar disappears from the tubular urine in passing through the *proximal tubule* so that the urine reaching Henle's loop no longer contains any glucose (if its content in the plasma and, consequently, in the primary urine does not exceed 170 to 200 mg. per cent);

b) less fluid reaches Henle's loop along the proximal tubule than the amount of glomerular filtrate entering the proximal tubule from the cavity of Shumlyansky's corpuscle. The amount of fluid further diminishes in Henle's loop. It follows that ***water is reabsorbed into the blood in the proximal tubule and in Henle's loop*** (mainly in ***its thin segment***). It has also been demonstrated that chlorides and urea pass into the blood from the tubular urine.

The proof that processes of reabsorption of sugar, water and urea occur in the tubules does not as yet solve the problem of the mechanism of urine production. If, for example, there is 120 times as much creatinine in the urine, which runs from the kidney into the urinary bladder,* as there is in the plasma it may be due to the fact that of the 120 ml. of the glomerular filtrate 119 ml. are reabsorbed into the blood, or that 80, 60 or 40 ml. of water has been reabsorbed into the blood and $\frac{2}{3}$, $\frac{1}{2}$ or $\frac{1}{3}$ of the excreted creatinine has been ***added*** to the tubular urine by ***secretion*** also of this substance from the blood into the urine by the cells of the tubular epithelium. This old hypothesis of Heidenhain and Gurvich of the secretion of various substances from the blood into the urine was always advanced when the mechanism of urine production was dealt with.

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* The urine undergoes practically no change in the ureters and in the urinary bladder, so that the composition of the urine voided from the body may be considered the same as that which leaves the nephrons. In other words, the entire process of urine production in mammals begins and ends in the nephrons (the mammals of lowest organization are an exception; like all birds and reptiles they have a cloaca from which water is absorbed into the blood).

The production of "finished" urine from the protein-free glomerular filtrate may, consequently, be explained in two ways: firstly, various amounts of different substances are added from the blood to the urine in the tubules and, secondly, during the passage of the urine along the tubules the water and various substances (necessarily in different proportions again) are reabsorbed from the urine into the blood. As regards sugar, reabsorption is an incontestable fact. At the same time in certain osseous fishes the constituents of the urine are, beyond all doubt, secreted from the blood into the tubular cavities. The kidneys of these fishes (angler) have no Shumlyansky's corpuscle with its glomerulus of capillaries and are, therefore, called *aglomerular*. The urine of fishes with aglomerular kidneys does not under any conditions contain any proteins or sugar (even if the content of the latter is raised to 400 or 500 mg. per cent) and the concentration of the compounds excreted from the body (for example, urea) is not proportional in the urine of these fishes to that in the blood plasma. Though aglomerular kidneys differ considerably from the kidneys of mammals it is, nevertheless, hard to suppose that the latter are entirely devoid of a mechanism which secretes substances from the blood into the urine. On the strength of this and on the basis of the possibility of dyes being excreted with the urine in a concentration 500 to 700 times as high as that in the blood the idea that there may be a mechanism of secretion in the kidneys of mammals has been repeatedly advanced.

To solve the problem of the existence and extent of secretion of certain substances from the blood into the urine of the higher animals and to form an idea of the rate of reabsorption it was necessary to develop a method of quantitative measurement of the rate of glomerular filtration.

Measuring Glomerular Filtration

If we designate the amount of blood plasma (in millilitres) *filtered* from the glomerular capillaries into the initial division of the nephron per minute as x ml. and the content of some compound y in milligrams per ml. of plasma as $C_{pl.\,y}$, the value $C_{pl.\,y} \times x$ will correspond to the number of milligrams of the given compound excreted from the plasma into the glomerular filtrate (primary urine) per minute.

Neither in man nor in animals can we collect all of the glomerular filtrate from Shumlyansky's corpuscles of all nephrons at the same time, i.e., we cannot directly measure the total amount of glomerular filtrate leaving the blood plasma per minute.* However, we can very easily determine the amount and composition of the "final" urine excreted from the kidneys either by collecting it during voluntary urination at equal intervals (15 to 30 minutes) or through a catheter inserted into the bladder.** It is clear that if we know the rate of urine excretion per minute and the concentration of some particular substance y in milligrams per ml. of urine we can easily determine the amount of this substance excreted by the kidneys with the urine per minute. It corresponds to $V \times C_{u.y}$, where $C_{u.y}$ is the concentration of the substance y in the urine (in milligrams per ml.) and V is the number of millilitres of urine excreted per minute. On the other hand, we know the concentration of substance y in the glomerular filtrate because it corresponds to $C_{pl.y}$, i.e., its concentration in the blood plasma.

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* The aforesaid microphysiological experiments may ensure the collection of the ultrafiltrate of the plasma from the cavity of *one* Shumlyansky's corpuscle, but there is nearly a million of these corpuscles in each kidney. It is clearly impossible directly to collect all of the primary urine simultaneously from all Shumlyansky's corpuscles.

** Urine can be continuously collected from animals if the urethral openings are sewn into the skin, according to the method proposed by I. Pavlov. In man fine catheters can be separately placed into each ureter with the aid of a cystoscope and the urine can, thus, be collected from each kidney separately. This is necessary in cases when one of the kidneys must be removed which should, of course, be done only after the normal functioning of the other kidney has been reliably ascertained.

We have already made mention of the fact that various substances may be reabsorbed into the blood from the tubules. In this case part of the substance y, which has passed into the initial division of the nephron with the glomerular filtrate, is reabsorbed from the tubules into the blood and, consequently, does not reach the terminal division of the nephron; it does not, therefore, get into the urine excreted from the body. In this case $C_{pl.y} \times x$ will be greater than $C_{u.y} \times V$ (x is the amount of glomerular filtrate produced per minute). The reverse is also possible, i.e., secretion of y from the blood into the urine. In that case, in addition to the quantity of the given compound, which passed from the plasma into the cavity of Shumlyansky's corpuscle, a certain amount of the same compound will be added to the tubular urine, secreted into it from the blood. Then, of course, $C_{pl.y} \times x$ will be less than $C_{u.y} \times V$.

But if we find a substance which after passing into the initial division of the nephron as a result of ultrafiltration into primary urine from the blood plasma is neither reabsorbed into the blood in the renal tubules nor secreted from the blood into the urine, for this substance (we shall designate it as a) $C_{pl.a} \times x$ will exactly correspond to $C_{u.a} \times V$. In this case it is easy to find the value of x:

$$x = \frac{C_{u.a} \times V}{C_{pl.a}}.$$

It follows that *if some particular substance* after passing with the glomerular ultrafiltrate of the plasma into the initial division of the nephrons *does not re-enter the blood from the tubular urine and is not secreted into the tubular urine from the blood throughout the remaining extent of the nephrons the concentration of this substance in the urine divided by its concentration in the plasma and multiplied by the amount of urine secreted per minute indicates the number of millilitres of glomerular filtrate produced per minute.* According to many available facts (Smith et al.) some (not numerous) substances—inulin and mannitol (in dogs also creatinine)—meet this requirement. They are not reabsorbed from the renal tubules into the blood nor secreted by the tubules from the blood into the urine. We shall call these substances *filtrometric compounds* for short, since the determination of their concentration in the urine and in the blood plasma makes it possible to measure the rate of glomerular filtration (if the amount of urine excreted by the kidneys per minute is known).

The coefficient of clearance of the blood plasma from any particular compound y is the value $\frac{C_{u.y}}{C_{pl.y}} \times V$ we have just considered. In various concrete cases the first letters of the respective substance are used instead of the letter y in designating the concentration of substances in the urine ($C_{u.}$) and in the plasma ($C_{pl.}$); inulin is, thus, designated as *in*, glucose as *gl*, etc. (The designations of $C_{u.in.}$ and $C_{pl.in.}$ mean "concentration of inulin in the urine" and "concentration of inulin in the plasma"). In general, the *coefficient of clearance* ($\frac{C_{u.}}{C_{pl.}} \times V$) corresponds to the amount of blood plasma in millilitres which contains the amount of the given substance excreted by the kidneys in one minute of flow. If, for example, $C_{u.\,ur.}$ for urea equals 20 mg. (1 ml. of urine contains 20 mg. of urea) during the secretion of 1.2 ml. of urine per minute the amount of urea excreted with the urine from the organism in one minute corresponds to $C_{u.\,ur.} \times V = 20 \times 1.2 = 24$ mg. If one ml. of plasma contains 0.3 mg. of urea the amount of plasma which contains the 24 mg. of urea excreted with the urine in one minute of flow is $\frac{20}{0.3} \times 1.2 = 80$ ml. For *filtrometric substances the coefficient of clearance corresponds to the rate of glomerular filtrate* because in this case the amount of substance excreted from the blood plasma into the glomerular filtrate in one minute of flow corresponds to the amount of the given substance excreted in one minute by the kidneys.

Inulin, a complex carbohydrate (molecular weight about 5,200) with a very low diffusion coefficient, is found only in plants; with sufficient purification it is not poisonous, can be injected intravenously and is easy to determine quantitatively in the urine and in the plasma. Mannitol (hexatomic alcohol) and titricine (polymer of fructose) are also filtrometric compounds; creatinine can serve the same purpose in dogs, but not in man.

Several methods demonstrate independently of each other that filtrometric substances are really not reabsorbed from the tubular urine into the blood and are not secreted by the tubules into the urine. Glucose is undoubtedly reabsorbed, but the reabsorption is fully blocked if phloridzin, a certain poison, is injected into the animal. Phloridzin does not stop the production of urine, but in an animal poisoned with phloridzin all of the glucose that passed into the cavity of the initial division of the nephron enters the urine. In this case the coefficient of glucose clearance, which corresponds to zero in the absence of glucose from the urine, equals the coefficient of clearance for inulin, mannitol and titricine (creatinine in dogs). It can hardly be supposed that these substances should be filtered with the same coefficient of clearance if they were reabsorbed or secreted by the tubular cells (various substances are usually secreted and absorbed at different rates).

It has furthermore been established that the "clearance" values for inulin, mannitol, and in dogs for creatinine (after phloridzin poisoning also for glucose, xylose and saccharose) do not alter even when very substantial changes in the concentration of these substances in the plasma occur. This is due to the fact that a change in the concentration of these substances in the plasma does not directly affect the rate of urine production. And as long as the amount of the excreted urine does not change it follows that the quantities of reabsorbed water do not change either. We can then say that a twofold increase of the inulin concentration in the plasma (and consequently, in the glomerular ultrafiltrate) will cause its concentration to double in the urine. It is clear that in this case the coefficient $\frac{C_{u.\,in.}}{C_{pl.\,in.}} \times V$ will not alter. On the other hand, for substances known to be reabsorbed and for those secreted by the tubules from the blood into the urine (see below) the value of "clearance" greatly varies with the changes in the concentration of these substances in the plasma.

In practice inulin "clearance" (i.e., the rate of glomerular filtration) is usually determined after an intravenous injection of inulin.

For this purpose a rather constant concentration of inulin of about 18 to 25 mg. per cent (mannitol—100 to 130 mg. per cent) must be produced in the plasma. Micturition over a period of 30 minutes is determined (it is best to collect the urine by a catheter), the amount of inulin (or mannitol) contained in one ml. of urine is calculated, this figure is multiplied by the amount of urine produced in one minute, and the product is divided by the mean figure showing the amount of inulin contained in the plasma in the beginning and at the end of the 30 minutes during which the urine was collected. Considering the differences in physique, which affect, in particular, the size of the kidneys, all figures of clearance are usually related to 1.73 $m.^2$, the mean figure characterizing the surface of the body. This is why after finding the "clearance" value for inulin (like all other indices which will be dealt with below) the resulting figure is divided by the value of the examined subject's body surface (see nomogram, Fig. 147) and the quotient is multiplied by 1.73 (calculation per square metre of body surface would prove more accurate).

The "clearance" for inulin or mannitol, i.e., the rate of glomerular filtration (for a body surface of 1.73 m.^{2}) constituting 130 ml. per minute (± 21) for men and 120 ml. (± 16) for women is accepted as the standard. This rate changes but little with variations in the value of micturition, whence it follows that the rate of urine production hardly depends on the rate of glomerular filtration. Thus, in one experiment with a change in micturition from 4.2 to 1.3 ml. per minute the rate of glomerular filtration dropped only from 122 to 120. The concentration of inulin was 96 mg. per cent per 100 ml. in both cases, but there was 2,762 mg. per cent inulin in the urine in the first case and 8.980 mg. per cent in the second case.

Normally glomerular filtration always exceeds 100 ml. per minute (in terms of 1.73 m.^{2} of body surface), whereas the rate of urine production is usually 0.8 to 2 ml. per minute (it may reach 10 ml. per minute only after an intake of a large amount of liquid). The amount of reabsorbed water corresponds to the clearance for inulin (or mannitol) minus the amount of urine produced in the meantime. Consequently, the determination of the rate of glomerular filtration warrants the important conclusion that more than 100 ml. of water per minute is usually absorbed in the tubules. More than 100 times as much primary urine is filtered from the plasma into the cavity of the initial division of the nephron as the amount of urine excreted by the kidneys during the same period of time. It is, therefore, clear why the rate of urine production normally depends but little on the rate of glomerular filtration. If reabsorption constitutes 99 per cent of the rate of glomerular filtration, a change from 100 to 200 ml. per minute in the latter will lead to an increase in urine production of only 1 to 2 ml. per minute. On the other hand, a decrease in the amount of the reabsorbed liquid from 99 to 90 per cent will cause a tenfold increase in urine production, from 1 to 10 ml. per minute, at a glomerular filtration of 100 ml. A slight change in the percentage of the liquid reabsorbed in the tubules (in relation to the total value of the glomerular filtrate) causes a very sharp change in diuresis. This is why the rate of urine production is determined mainly by the intensity of tubular reabsorption.

Measuring Tubular Reabsorption

Reabsorption of water corresponds to the glomerular filtration (measured as a coefficient of clearance for one of the filtrometric substances) minus the amount of urine excreted by the kidney in one minute of flow. As was said above, more than 100 ml. of water per minute is usually reabsorbed in the tubules with 80 to 90 per cent of this amount reabsorbed into the blood already in the proximal division of the convoluted tubules.

The essential part in this is played by the oncotic pressure of the proteins in the blood plasma flowing through the capillaries which entwine the tubules. The blood pressure in them is very low because the blood flowing along the capillaries has already passed through the glomerular capillaries and the thin efferent vessel (*vas efferens*). The concentration of proteins in the plasma of the capillaries, which entwine the tubules is higher than in the blood of all the other capillaries of the body because about 15 to 25 per cent of the blood plasma has passed into Shumlyansky's corpuscle leaving its protein in the blood stream. Owing to this the oncotic pressure in the capillaries which entwine the tubules is higher than that of the blood, and the water from the tubular urine is drawn into the capillaries. Reabsorption of the water from the tubular urine into the blood is, thus, based partly on the physicochemical processes of water diffusion from the region of lower osmotic pressure to that of higher pressure through the epithelium of the tubules and their capillaries which act as a semipermeable membrane. If pure water without the substances dissolved in the tubular urine is absorbed from the urine into the blood the concentration of these substances will obviously immediately increase and the osmotic pressure of the tubular urine will exceed that of the blood in the tubular capillaries. Purely physicochemical absorption of water is, therefore, possible only if the substances dissolved in the urine are absorbed with the water in such quantities that the osmotic pressure of the absorbed fluid equals that of the blood plasma.

It is believed that 80 to 90 per cent of the water is absorbed into the blood in the proximal convoluted tubules in the form of an iso-osmotic solution. At the same time part of the sugar and of the ions of sodium and chlorine is absorbed into the blood because of the vigorous activity of the epithelium of the proximal division of the tubules, while urea passes from the tubules into the blood by diffusion.

Part (about 15 to 20 per cent) of the water is reabsorbed from the tubules into the blood by some active process the mechanism of which is not yet clear; this process ceases if the metabolism of the tubular epithelium is disturbed by cooling or by action of cyanides. This active absorption of water from the urine into the blood takes place in the thin segment of Henle's loop; in animals lacking this segment of the nephron the osmotic pressure of the urine never exceeds that of the blood plasma.

The general rate of urine production (from one year of age) depends mostly on the rate of active reabsorption of water in the thin segment of Henle's loop. The antidiuretic hormone, produced by the posterior lobe of the hypophysis (p. 430), sharply increases this active reabsorption of water which leads to a decrease in diuresis.

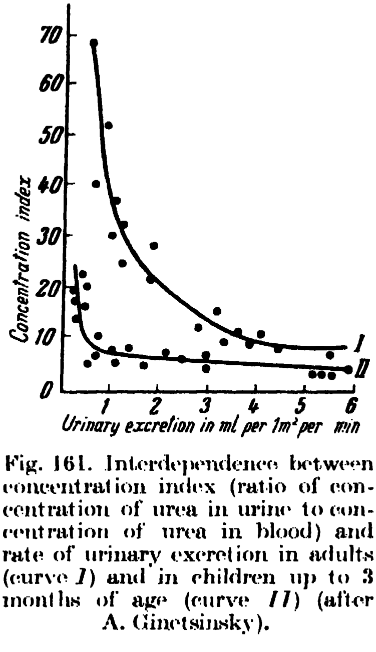

Fig. 161. Interdependence between concentration index (ratio of concentration of urea in urine to concentration of urea in blood) and rate of urinary excretion in adults (curve *I*) and in children up to 3 months of age (curve *II*) (after A. Ginetsinsky).

The more active the absorption of water in the tubules the higher the so-called *concentration index* (relation of the concentration of urea in the urine to that in the blood). A decrease in urine production due to increased reabsorption of water leads to a rise in this index (Fig. 161). The active absorption of water in children under one year of age does not reach the rate observed in later years.

Substances with high and low thresholds of elimination. Some substances—urea, sulphates and all foreign substances—continuously pass from the blood into the urine, however small the amounts the blood contains. These are substances with a low threshold of elimination. They are reabsorbed in relatively small quantities and the urine, therefore, contains them in greater concentration than does the blood plasma. If the diffusion coefficient of such substances as, for example, SO_4'' ions is very low they are hardly reabsorbed, whereas the anions, which do not pass from the tubular urine into the blood, infallibly retain an equivalent number of cations in the urine. The sum total of the cation charges in the urine is thus equal to that of the anion charges.

For all substances passing from the plasma into the cavity of Shumlyansky's corpuscle the $C_{pl.\,y} \times x$ corresponds to the amount of the given substance passing into the glomerular filtrate in one minute of flow, if x designates the coefficient of inulin clearance equal to the rate of glomerular filtration. It is clear that the amount of substance reabsorbed per minute corresponds to $C_{pl.\,y} \times x - C_{u.\,y} \times V$.

Reabsorption and elimination of glucose. The urine of people with a normal carbohydrate metabolism contains no glucose (nor fructose or any other carbohydrates) if the content of sugar in the blood does not exceed 170 to 200 mg. per cent. At the same time there is always as much glucose in the glomerular filtrate as in the plasma.

Reabsorption of glucose is connected with the production of hexosephosphoric acid (as an intermediate product) in the cells of the tubular epithelium. Nonphosphorylating monosaccharides, for example xylose, are reabsorbed into the blood in very negligible quantities only because of reverse diffusion.

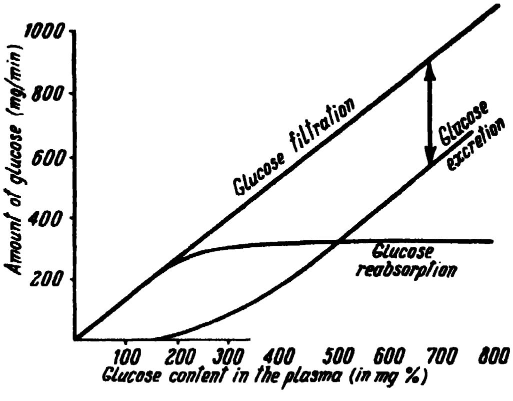

Fig. 162. Urinary excretion of glucose, glucose reabsorption and its filtration in the glomeruli depending on glucose content in blood (after Fulton).

Glucose appears in the urine flowing into the bladder only when its concentration in the blood exceeds the threshold of 170 to 200 mg. per cent. Beginning with the threshold of elimination, i.e., a definite concentration of glucose in the blood plasma, elimination of glucose with the urine rapidly increases.

The amount of reabsorbed glucose corresponds to the difference between the amount of glucose filtered from the plasma into the initial division of the nephron in one minute of flow and the amount of glucose excreted with the urine per minute. Hence $R_{gl.} = C_{gl.\,p.} \times x - C_{gl.\,u.} \times V$, where R is the amount of glucose in milligrams reabsorbed per minute and x is the rate of clearance for inulin. By determining the rate of $R_{gl.}$ (reabsorption of glucose in the tubules per minute) it has been possible to show that after the glucose begins to be eliminated from the body a direct proportion between the excretion of glucose by the kidneys and its content in the blood is rapidly established (Fig. 162). The rate of reabsorption then becomes constant (else the excretion of glucose would not be directly proportional to its concentration in the blood). The maximal rate of glucose reabsorption constitutes about 300 to 350 mg. per minute (Fig. 162). Determination of this rate (after injecting large amounts of glucose into the blood) offers a certain characteristic of the condition of the renal tubules.

Tubular Secretion

Estimation of the rate of glomerular filtration by the coefficient of inulin clearance made it possible to solve the problem of whether the cells of the tubules secreted any substances from the blood into the urine. It will be remembered that the coefficient of clearance for inulin shows the amount of ultrafiltrate filtered through the wall of the glomerular capillaries into Shumlyansky's cavity in one minute of flow. If the coefficient of clearance for any substance turns out to be higher than the rate of glomerular filtration, i.e., greater than the inulin clearance (x), it means that this substance is added from the blood to the urine while the latter flows along the tubules. It appears that several compounds have a much higher coefficient of clearance than that for inulin or mannitol. They include certain dyes (for example, phenol red), penicillin, para-aminobenzoic acid and diodrast, an iodine compound used in X-raying the kidneys. The coefficient of clearance for these substances may reach 400 to 800, i.e., exceed the coefficient of inulin clearance (glomerular filtration) from three- to sevenfold.

Determination of the coefficient of clearance for substances secreted by the epithelium of the tubules from the blood into the tubular urine shows that with an increase in the concentration of these substances in the blood plasma the coefficient of their clearance from the plasma, which is always higher than the coefficient of inulin clearance, begins to drop approaching the inulin clearance as a limit. This is due to the fact that there is a certain limited amount of substance more than which the cells of the tubular epithelium cannot secrete per unit of time. At the same time the amount of excreted urine does not essentially change with an increased concentration in the blood of the substances eliminated from the latter not only by filtration, but also by secretion.

The cells of the tubular epithelium secrete certain substances from the blood into the urine, for example, para-aminohippurates and diodrast, extremely intensively. Experiments, in which the content of these substances in the plasma of the arterial blood and in the renal vein was being chemically determined, have shown that the blood running along the tubular capillaries liberates all of the para-aminohippurates and the diodrast, whereas the blood which flows to the kidneys along the renal artery liberates approximately 90 per cent of these compounds (about 10 per cent of the blood flowing through the kidneys apparently does not run through the nephrons and does not, therefore, give off the substances it contains into the urine).

If, owing to the processes of tubular secretion, the blood plasma, running through the kidneys, liberates approximately 90 per cent of certain substances (diodrast and para-aminohippurates), secreted into the urine by the cells of the tubular epithelium, it enables us to estimate the amount of plasma and, consequently, of the blood flowing through the kidneys per minute. This is possible because in this case the concentration of such a substance in the plasma of the arterial blood corresponds to the amount of this substance liberated by each 100 ml. of plasma which flows through the kidneys. If, say, the arterial plasma, which can be taken for analysis by puncturing any artery, has 10 mg. per cent diodrast, and the plasma of the blood, which has flown through the kidneys, i.e., the blood from the renal vein, shows no diodrast at all, it follows that each 100 ml. of plasma gives off 10 mg. of diodrast while flowing through the kidneys. If the total excretion of diodrast with the urine is, say, 60 mg. per minute it is clear that $(60:10)\times 100$, i.e., 600 ml. of plasma has flown through the functioning renal nephrons in one minute. It is easy to see that we have again the value of the coefficient of clearance, this time determined by the use of diodrast (para-aminohippurates can also be used). Thus, the clearance of diodrast or for para-aminohippurates gives us a sufficiently accurate measure of the amount of plasma flowing through the renal nephrons per minute (transition from this value to the amount of blood is very easy if we estimate the relative volume of the plasma and the blood corpuscles with the aid of haematocrit).

Estimation of the blood flow (the "plasma flow," to be exact) through the kidneys by the rate of the clearance of para-aminobenzoic acid or diodrast has shown that 700 ± 130 ml. of plasma normally flows through both kidneys in men and 600 ± 100 ml. in women (all figures are given in terms of 1.73 m.^{2} of body surface) per minute. The amount of blood flowing through the kidneys constitutes about 1,000 to 1,200 ml. per minute which at rest equals approximately 15 to 20 per cent of the total blood pumped by the heart into the aorta per minute. It is only because of this abundant blood supply that the process of urine production is possible, since it requires the filtration of 100 to 150 ml. of the ultrafiltrate from the blood plasma per minute.

It is clear that the entire plasma cannot filter into Shumlyansky's cavity under any circumstances, else the capillaries would be blocked by a dense blood residue. The ratio of the rate of glomerular filtration to the rate of the "plasma flow" through the kidneys shows the part of the plasma that filters from the glomerular blood stream into the cavity of the initial division of the nephron (and then largely reabsorbed). This value is usually 15 to 25 per cent.

CHAPTER 37

RATE OF URINE PRODUCTION AND REGULATION OF RENAL ACTIVITY

Rate of Urine Production

The amount of urine normally produced by the kidneys per unit of time (*diuresis*) is determined mainly by the content of water in the body, the rate of metabolism and factors affecting the elimination of water through extrarenal channels. Normally the content of water in the body is quite constant and any intake of superfluous quantities of liquid leads to an increased elimination of water. It has already been said that a relatively small amount of water is excreted through the skin (by perspiration and invisible evaporation) and through the lungs with the vapours which saturate the expired air. The main mass of the water drunk, contained in the foods consumed and produced in metabolism, is eliminated by the kidneys. The amount of urine eliminated in these cases quite closely corresponds to the quantity of water taken in by the body. But if a great deal of water is given off through the skin and the lungs, as is the case in considerable perspiration caused by high temperature or hard muscular work, less urine is secreted and a considerable part of the water entering the body is eliminated extrarenally.

The amount of urine normally produced by the kidneys per day at an environmental temperature of 20°C with the average diet and excluding hard work constitutes about 1.2 to 1.5 litres.

Reaction of kidneys to water intake. Normally the kidneys react to changes in the water content in the body so keenly that after an intake of 1 to 1.5 litres of water it takes the kidneys 3 to 6 hours to eliminate it with 75 per cent of it eliminated during the first 2 hours. Figure 163 shows typical urine production after an intake of water; the diagram shows that an increase in the production of urine (diuresis) begins approximately 30 to 50 minutes after drinking, while 1.5 to 2 hours after the intake of liquid the amount of urine produced begins to diminish approaching the values characteristic of urine production before the intake of liquid.

Urine production when no liquid is taken in. If no liquid is taken in over a certain period of time the loss of water excreted through the kidneys becomes a factor which disturbs the constancy of the water content in the body. Since the products formed as a result of the never ceasing transformations of proteins (urea, etc.) can be eliminated only dissolved in water the kidneys never stop producing urine, but with no liquid ingested relatively little urine is produced (approximately 15 to 30 ml. per hour). In scanty urine production the concentration of urea and salts in the urine is high and this leads to an increase in the specific gravity of the urine.

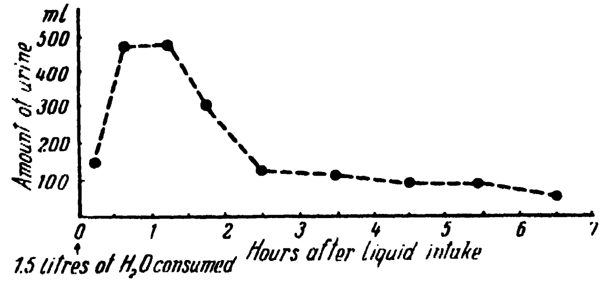

Fig. 163. Changes in diuresis after drinking water. Along ordinate—rate of diuresis (in ml. in 15 minutes); along abscissa—time after liquid intake.

Regulation of Renal Function

In normal work of the kidneys the amount and composition of the urine depend on the intensity of water, nitrogen and salt metabolism. The regulation of renal function finds its most vivid expression in a sharp increase in diuresis after a liquid intake and in its limitation (with an excretion of concentrated urine) when no liquid is taken in.

Regulation of renal function by the higher nervous system is characterized by a number of interacting processes which can, in a certain measure, replace each other. This regulation is effected by nerve impulses transmitted directly to the kidneys and through the hypophysis; one of the hormones of the latter influences the production of urine.

Effect of hormone of posterior lobe of hypophysis on kidneys. It has been found that extracts from the posterior lobe of the hypophysis decrease the production of urine in the body as a whole (after an injection of pituitrin, extract of the posterior lobe of the hypophysis) and in the isolated kidney through the vessels of which blood with an addition of the extract of the hypophysis is perfused. The decrease in the production of urine is accompanied by an increase in the concentration of the substances contained in the urine.

The decrease in the production of urine effected by the hormone of the posterior lobe of the hypophysis is due to the fact that this hormone sharply increases reabsorption of water in the thin segment of Henle's loop. The hormone of the posterior lobe of the hypophysis does not decrease the production of urine in animals lacking this division of the nephron.

By increasing the reabsorption of water in the convoluted tubules the hormone of the posterior lobe of the hypophysis simultaneously decreases the reabsorption of sodium and potassium ions from the tubular urine. As a result the content of sodium and potassium in the urine increases which leads to a retention of an equivalent amount of anions, primarily of chlorine, in the urine. Some authors consider the hormone of the posterior lobe of the hypophysis which decreases the production of urine identical with vasopressin.

Effect of hormones of adrenal and other endocrine glands. The hormone of the cortex of the adrenals increases the reabsorption of sodium ions in the tubules. The deficiency of this hormone, after removal of the adrenals, leads to a considerable loss of sodium by the organism, which is responsible for the decrease in the ratio of the concentration of sodium and potassium in the blood plasma. A plentiful supply of NaCl to animals with removed adrenals considerably prolongs their life.

The parathyroid hormone increases the elimination of phosphoric acid from the blood into the urine.

There are indications that the functions of the kidneys are influenced by the thyroid and the anterior lobe of the hypophysis.

The influence of the nerves on renal function could not be reliably ascertained for a long time since the methods used in studying the nervous influences on any particular organ failed to produce any dependable results in this case; electric stimulation of the nerve fibres running to the kidneys usually led to a decrease in diuresis, but this could be explained by the constriction of the afferent vessels caused by stimulation of the vasoconstrictor nerve fibres. Severance of all the nerve fibres running to the kidneys does not lead to sharp diuretic disturbances. Even a kidney grafted on the neck (with the renal artery sewn to the carotid artery and the renal vein to the cervical vein) retains the ability to react to an excess of water by a considerable increase in diuresis. In this grafted kidney, which is, consequently, disconnected from the central nervous system, an increase in the content of urea and salts with a sharp limitation in the production of urine is also observed since no water enters the organism. An idea, that the nervous influences transmitted to the kidneys along the afferent nerve fibres are of no essential importance to renal function, was even advanced on the strength of these experiments. But the use of Pavlov's principles of investigating the whole organism in studying the functions of the kidneys enabled K. Bykov to ascertain that the production of urine is always controlled by the influences of the cerebral cortex. This finds proof in the fact that the work of the kidneys is regulated by conditioned reflexes easily developed to renal function if an agent formerly entirely indifferent in its effect on the kidneys is combined with the action of a stimulus which directly affects renal function. Thus, for example, if the sound of a trumpet is accompanied several times by an infusion of water into the stomach, after this combination is repeated several times the sound of the trumpet alone, unaccompanied by an infusion of water, causes approximately the same increase in the production of urine as the unconditioned stimulus—the infusion of liquid into the stomach (Fig. 164).

Mechanism of cortical influence on kidneys. The cortical stimuli resulting from conditioned reflexes may be transmitted to the kidneys in two ways: 1) nerve impulses arising in the cortex are propagated along afferent nerve fibres to the renal tissue and directly stimulate the kidneys; 2) nerve impulses arising in the cortex are transmitted to the hypophysis along nerve fibres innervating its posterior lobe and alter the secretion of the antidiuretic hormone into the blood. This capacity of the cerebral cortex to influence renal function in two ways is demonstrated by the fact that after denervation of one of the kidneys (when all of its afferent nerves are cut) the stimuli, which were combined with the infusion of water into the animal, are still able to stimulate production of urine because of the conditioned reflex acting on the kidney. But no conditioned-reflex increase in diuresis can be produced in the *denervated* kidney if we add an injury to the nervous connections of the hypophysis with the central nervous system to the denervation of the kidney, while in the kidney, which retains direct nervous connections with the central nervous system, the stimuli preceding the infusion of water into the organism cause a conditioned-reflex increase in diuresis even after the disconnection of the hypophysis.

These experiments conducted in K. Bykov's laboratory show the existence of direct nervous influences on the kidneys (since conditioned-reflex regulation of renal function is also possible after disconnecting the hypophysis) and reveal the possibility of complex conditioned-reflex regulation of renal function in which the conditioned-reflex connection between the cerebral cortex and the hypophysis (through subcortical structures) comes to the fore. In this case we have direct conditioned-reflex influence on the hypophysis. Due to the development of a conditioned reflex to the hypophysis the stimulus, say, the sound of a trumpet reinforced by the infusion of water, causes the same decrease in the secretion of the hormone of the posterior lobe of the hypophysis into the blood as does the infusion of water into the organism. A decrease in the content of the pituitary hormone which increases reabsorption of water (i.e., decreases diuresis) causes an increase in the production of urine. In this case we thus have a neurohumoral cortical mechanism regulating renal function.

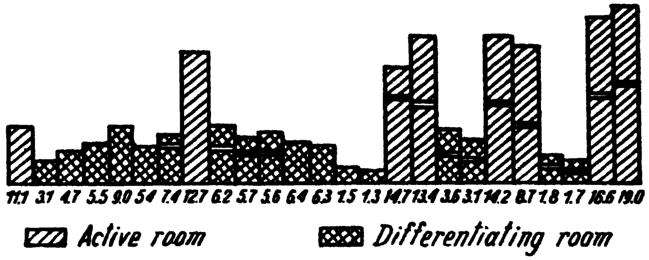

Fig. 164. Changes in diuresis in the dog under conditions in which water was repeatedly infused into the animal's stomach ("active room") and under conditions in which water was never infused ("differentiating room").

Each column shows amount of urine excreted during two-hour experiment; figures under columns show amount in millilitres. It can be observed that under conditions which were a signal for water infusion excretion of urine was greater (due to development of conditioned reflex for the kidneys) than under conditions in which no water was infused (after K. Bykov).

Severance of all efferent nerves of the kidneys causes certain changes in renal function with a somewhat slower than normal increase in diuresis after an intake of excess water and a somewhat greater production of urine with no liquid taken in.

The neurohumoral mechanism of regulating pituitary activity cannot, consequently, fully replace the direct nervous influences transmitted to the kidneys along the efferent fibres of the splanchnic nerve (and, probably, partly the vagi).

It has been shown in the laboratory headed by A. Ginetsinsky that in animals during the first days of their life, when the humoral influences on the kidneys are not so strongly pronounced, denervation of one kidney frequently leads to degeneration of the renal parenchyma which is replaced by connective tissue.

Mechanism of changes in renal function with excess intake of water. The inborn (unconditioned) mechanism of increasing diuresis consists in the fact that in being absorbed into the blood water very slightly dilutes the latter. In this case the concentration of the salts in the blood plasma somewhat decreases. The interoceptors of the vascular system include osmoreceptors (Bykov, Verney) stimulated by changes in the osmotic pressure of the blood plasma. Such osmoreceptors have been discovered, in particular, in the system of the internal carotid artery (Richards). Suffice it to inject a small amount of a hypertonic sodium chloride solution into the internal carotid artery to cause reflexly an increased liberation of the antidiuretic pituitary hormone into the blood and a decreased diuresis. Contrariwise, a slight drop in the osmotic pressure of the blood plasma which bathes the osmoreceptors of the cerebral vessels reflexly inhibits the secretion of the antidiuretic hormone thus leading to an increase in diuresis. But the delay in the secretion of the antidiuretic hormone does not at once lead to a rise in diuresis since the blood has "reserves" of the formerly secreted antidiuretic hormone. This is why 40 to 50 minutes usually pass between the ingestion of water into the organism (even if water is ingested directly into the blood stream) and the beginning of an appreciable rise in diuresis; it is the time required for the antidiuretic hormone, which was in the blood before the ingestion of water, to be eliminated.

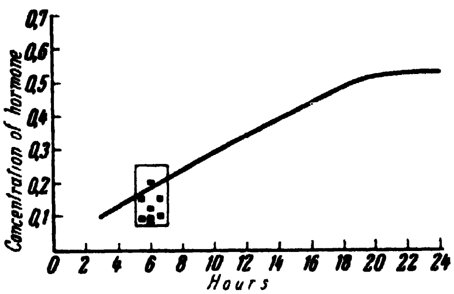

Fig. 165. Content of antidiuretic hormone in urine depending on the period during which no liquid was consumed.

Along ordinate concentration of antidiuretic hormone in urine (in relation to the unit), along abscissa—number of hours after last fluid intake. Rectangle shows zone of fluctuation in concentration of antidiuretic hormone in urine of an adult after 6 hours during which no liquid was consumed. Black squares in rectangle show corresponding rates for children up to 8 months of age.

The antidiuretic hormone secreted into the blood by the posterior lobe of the hypophysis is partly eliminated from the body through the kidneys with the urine. Concentration of this hormone in the urine is the higher the more of it is contained in the blood. The longer man has not taken in any liquid the more antidiuretic hormone is excreted (Fig. 165) with the urine (A. Ginetsinsky et al.). Consequently, after each intake of liquid less antidiuretic hormone of the hypophysis is secreted into the blood; limitations in liquid intake increase the secretion. This reflex regulation of the secretion of the antidiuretic hormone into the blood plays a most important part in the increase of diuresis after a liquid intake and in its sharp decrease during a water deficiency in the organism.

It is possible that the origin of nerve impulses acting directly on the kidneys by their efferent fibres is also conditioned by the reflexes from the vascular osmoreceptors. The latter are stimulated by the insignificant drop in the osmotic pressure of the blood plasma which results from the dilution of the blood by the absorbed water.

Normally the unconditioned reflexes, which influence renal function, are inseparably interlinked with the natural conditioned reflexes developed on their basis. Water drinking and all the stimuli connected with the intake of water (also, of course, beer, tea and other beverages), therefore, stimulate renal function determining the normal reaction of the kidneys to water intake. This manifests itself, in particular, in the fact that after an intake of water by mouth diuresis nearly always increases more than when the same amount of water is imperceptibly ingested through a tube into the stomach.

The interoceptors of the kidneys are, probably, also stimulated in the process of renal function. The resultant afferent impulses may reflexly influence the work of the kidneys. This question, however, is not clear as yet.

Mechanism of diuresis caused by salts, glucose and other agents. A rise in the osmotic pressure of the urine flowing along the tubules decreases reabsorption. With the osmotic pressure of the tubular urine approaching 20 atmospheres the water in the kidneys is reabsorbed ever more slowly and ceases to be reabsorbed when the osmotic pressure in the urine reaches 22 to 24 atmospheres. Reabsorption of water from the urine into the blood slows down and more urine is thus produced when the concentration of the dissolved molecules (and ions) in the tubular urine rises. If, for example, the concentration of glucose in the blood plasma (and, hence, in the primary urine—the ultrafiltrate of the plasma) is higher than about 0.2 per cent, the excess of glucose is not reabsorbed from the tubular urine, the osmotic pressure of the urine rises and as a result reabsorption of water from the urine decreases and diuresis increases. This is observed in diabetes and after an injection of glucose into the blood when the concentration of glucose in the blood and in the ultrafiltrate of the plasma sharply rises. A rise in the osmotic pressure of the urine is also observed after injections of sulphates (Na_2SO_4 and $MgSO_4$) into the blood; the sulphates are scarcely reabsorbed. It may be wrong, however, to explain the diuretic effect of the injections of glucose and sulphates into the blood by physicochemical factors alone since even with 2 per cent glucose in the urine the osmotic pressure of the latter rises approximately by only 2.5 atmospheres.

An increase in diuresis is also observed after an intake of caffeine and certain mercurials. The influence of the former is explained by a greater flow of blood to the kidneys; the influence of the latter is thought to be due mainly to an increased passage of water from the tissues into the blood.

Maximal concentration capacity of kidneys. All metabolites and salts eliminated by the kidneys can be excreted only in the form of aqueous solutions. With no water taken in by the body the maintenance of a constant internal environment requires maximum water retention, i.e., excretion of urine of highest possible concentration. When the reabsorption of water in the tubules and the secretion of certain substances from the blood (of the normally found substances, apparently, creatine and potassium—E. Asratyan) lead to an ever-greater concentration of the urine, the osmotic pressure of the latter, as it flows along the tubules, increases. The cells of the tubular epithelium (thin segment) resist this osmotic pressure of the tubular urine for some time, but then comes the moment when further absorption of water from the urine, which has become sharply hypertonic in relation to the blood, is no longer possible. In man the osmotic pressure of the urine never exceeds 25 atmospheres (compared with the 7.2 to 7.6 atmospheres of the osmotic pressure of the blood plasma). Twenty-five atmospheres is the osmotic pressure of an approximately 6 per cent solution of urea. Since, in addition to the latter, the urine always contains salts (even when no food or liquid are taken in they constitute at least 1 per cent of the urine) it may be said that the body cannot excrete more than 4 to 4.5 gr. of urea per 100 ml. of urine (in children the concentration capacity of the kidneys during the first months of life is lower). With a diurnal production of at least 20 to 30 gr. of urea man cannot, therefore, rid himself of the products of nitrogenous metabolism if less than 400 to 500 ml. of urine is produced per day. Any impairment of renal function affects the capacity of the kidneys to reabsorb water. The degree of urine concentration, when no liquid is ingested (during complete starvation or dry-eating), therefore, serves as a certain index of renal efficiency. Since a 0.23 per cent increase in the urea content of the urine raises the specific gravity of the urine by approximately 0.001, the value of the specific gravity of the urine excreted after 12 hours of starvation or dry-eating is an index of the renal concentration capacity. A healthy body, during dry-eating or starvation, produces only 20 to 30 ml. of urine per hour, but the specific gravity of this urine is between 1,020 and 1,030 with a 2.5 to 4 per cent urea content. Disorders of the renal function manifest themselves in a decreased capacity of the epithelium of Henle's loop for reabsorbing water from the tubular urine into the blood. This may be due not only to an impairment of the cells of the tubular epithelium, but also to disorders of the regulation of renal function. The body rids itself of the "slags" of nitrogenous metabolism only by losing large amounts of water because in these cases elimination of concentrated urine is impossible and the body excretes a large quantity of urine with a low urea content and a specific gravity only a little higher than that of the blood plasma. The test of the concentration capacity of the kidneys by determining the amount and specific gravity of the urine excreted by man after 12 to 16 hours of complete starvation (or taking food that does not contain any water, for example, dehydrated curds or dry bread), proposed by the prominent Russian clinicist S. Zimnitsky, is, therefore, a valuable method of diagnosing the condition of the renal function.

Anuria

Failure to produce urine is called *anuria* (a considerable decrease in the production of urine is known as *oliguria)*. Anuria inevitably leads to death within 4 to 6 days because of intoxication by the products of nitrogenous metabolism and potassium salts which are not excreted with the urine. It is not quite clear as yet what substances cause the severe symptoms of anuria (convulsions, weakening of the cardiac function and coma, i.e., paralysis of the higher nervous centres). It is, apparently, not a matter of urea alone. The retention of a number of products of protein metabolism, whose structure is as yet unknown, and of certain products of protein putrefaction in the intestines absorbed into the blood and usually excreted with the urine is, probably, of the greatest importance. Considerable importance in the symptoms of anuria is lately being ascribed to potassium ions whose increased content in the blood leads to acute disorders of the cardiac function.

In anuria the skin and intestines eliminate a much larger amount of urea with the sweat and with the secretions entering the intestines than normally. This cannot, however, replace the deficient excretory function of the kidneys. Artificial "vivodiallyzers" have been proposed; these are a system of tubes in which the blood is separated from pure water all along by various artificial membranes impermeable to proteins, but penetrable to all other products of nitrogenous metabolism and to salts. Such an artificial kidney is connected with one of the arteries (the blood is prevented from coagulating by heparin); excessive loss of water and salts is compensated by their addition to the food. This method has kept animals alive for 3 to 4 weeks after removal of the kidneys. The method is likely to find application in the clinic in reversible renal disease when it is necessary to save the life for a few days until the renal epithelium regains relative normalcy (for example, in poisoning with salts of mercury).

Momentary anuria (usually not dangerous to life) develops in response to harmful stimuli (for example, a painful puncture, application of electric current to the skin) and to signals of such stimuli. It has been demonstrated in L. Orbeli's laboratory that such *reflex anuria* is caused mainly by a vigorous secretion of an antidiuretic hormone into the blood.

CHAPTER 38

ELIMINATION OF URINE AND EXTRARENAL EXCRETORY PROCESSES

Functions of Ureters and Bladder

The urine flows along the ureters by peristalsis of the latter's smooth muscles. There are from one to five peristaltic contractions per minute, the contractions propagated along the ureters at the rate of 2 to 2.5 cm. per minute.

The smooth muscles of the bladder are arranged in three layers; the middle layer consists of circular fibres; the inner and outer layers, of fibres running parallel to the long axis of the bladder. At the site where the urethra leaves the bladder the circular muscles are thicker and embrace the initial part of the urethra (*m. sphincter vesicae*). The rest of the muscle fibres of the bladder are called the *detrusor* muscle. In the male the membranous portion of the urethra is surrounded by a striated muscle (*m. sphincter urethrae membr.*) which forms the outer sphincter. The *m. bulbo-cavernosus* plays the same part. In the female the role of these muscles is partly played by the smooth circular muscles in the walls of the urethra. The *detrusor* and the *m. sphincter vesicae* exert antagonistic influences on the filling of the urinary bladder. In contracting the smooth muscles of the bladder develop a pressure which is transmitted to the urine filling the bladder. This factor ensures emptying of the bladder, whereas the circular muscles of the sphincter, when contracted, constrict the urethra and do not let the urine flow to the exterior.

The bladder empties normally when the *detrusor* muscle contracts and the sphincter simultaneously relaxes. Retention of the urine requires relaxation of the *detrusor* and a contraction of the sphincter.

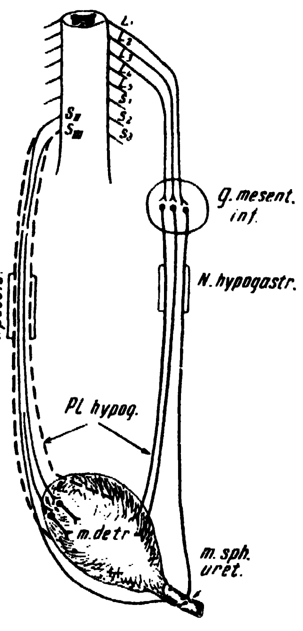

Fig. 166. Diagram of innervation of urinary bladder. Left parasympathetic, right sympathetic innervation of urinary bladder.

1 li sh afferent fibres.
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Innervation of muscles of urinary bladder. The motor fibres for the *detrusor* muscle are the *parasympathetic* nerve fibres of the sacral division of the vegetative nervous system. The cell bodies of the neurons which give off preganglionic fibres of this division of the parasympathetic system are in the 2nd and 3rd sacral segments of the spinal cord. The preganglionic parasympathetic fibres run in the pelvic nerves and come in contact in the wall of the bladder with the cell bodies of the second neuron whose short axons form the postganglionic parasympathetic fibres. These fibres stimulate the *detrusor* and inhibit the sphincter of the bladder (Fig. 166).

The motor fibres of the *sphincter* of the bladder are *sympathetic* nerve fibres; the postganglionic fibres innervating the sphincter are axons of the neurons located in the hypogastric ganglion. The preganglionic sympathetic fibres which come in contact with the cells of this ganglion are axons of the sympathetic cells located in the 1st-3rd lumbar segments of the spinal cord. These preganglionic sympathetic fibres run to the hypogastric ganglion in the inferior mesenteric plexus and the superior and inferior hypogastric plexes.

The sympathetic fibres simultaneously cause the sphincter to contract and inhibit the work of the detrusor. This may be presented schematically as follows:

	Sympathetic fibres	*Parasympathetic fibres*
M. detrusor	Inhibit	Stimulate
M. sphincter vesicae	Stimulate	Inhibit

The afferent fibres from the urinary bladder travel in the pelvic and hypogastric nerves, while the afferent fibres of the urethra run in the pudendal nerve. The fibres which transmit the impulses of pain from the bladder and the urethra travel only in the pelvic nerve.

Mechanism of Micturition

One of the properties of smooth muscles, especially strongly pronounced in the muscles of the urinary bladder, is the ability to stretch to a certain limit without appreciably changing their tension. Whether there are 10, 30 or 100 ml. of urine in the human bladder the pressure in its cavity will hardly change without the impulses which cause the bladder to contract. On the other hand, should the amount of liquid go beyond a certain value (which varies with the physiological states of the bladder) the pressure in its cavity will rise and drop sharply during micturition (Fig. 167).

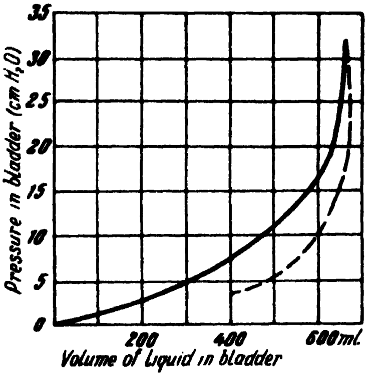


Fig. 167. Pressure in urinary bladder (continuous line) depending on its distention; fall of pressure (dotted line) during emptying of bladder (after Denny-Brown).

Distention of the bladder acts as a natural stimulus for the receptors located in the wall of the bladder. Stimulation of these receptors *reflexly* causes the detrusor to contract and the sphincter to relax. This is the *micturition reflex*.

The detrusor usually contracts reflexly when the pressure in the cavity of the bladder rises to 12-15 cm. H_2O and the bladder is distended with 200 to 250 ml. of urine. If, however, the flow of the urine into the bladder is fast (high diuresis) the pressure in the bladder reaches 12 to 15 cm. H_2O with a lesser filling of the bladder than when it is distended slowly at a low diuresis. A desire for micturition is experienced only when the pressure of the liquid in the bladder reaches a certain value. The desire to micturate is accompanied by respiratory changes and changes in the potentials of the skin (Figs. 168 and 169) so that micturition, like all normal reflex acts, is connected with the functions of a number of effectors.

Contractions of the *detrusor* may not lead to micturition if the sphincter remains contracted. The most acutely experienced desire to micturate is, probably, connected with the period when the contractions of the *detrusor* do not lead to an emptying of the bladder because of the failure of the sphincter to relax. These contractions soon cease, to be resumed with the further distention of the bladder.

The normal act of micturition is aided by:

a) a rise in pressure in the bladder caused by contractions of the abdominal muscles. This forms the basis for the ability to empty the bladder at will when there are small amounts of urine in the bladder (by "straining" oneself);

b) reflexly increased contractions of the detrusor muscle produced by stimulation of the receptors in the urethra during the passage of urine;

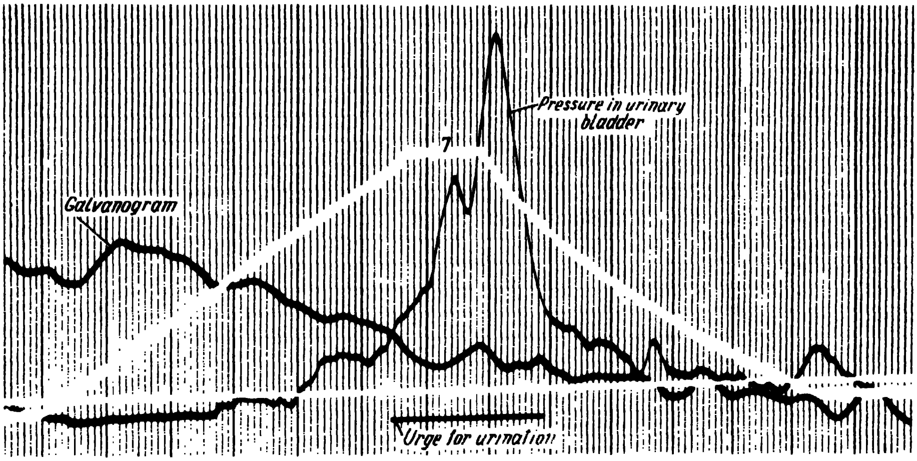


Fig. 168. Contractions of urinary bladder muscles during "sham-infusion of liquid into bladder," i.e., during rise in the liquid pressure in manometer located before person examined. Formerly the rise in pressure in the manometer corresponded to real distention of bladder by liquid infused into it. It can be observed that with a rise in pressure in the manometer to figure 7 pressure in urinary bladder begins to rise. Urge for urination appears and the skin potential changes simultaneously (galvanogram) (after E. Airapetyants).

c) relaxation of the external sphincter (in the male) and the *m. bulbocavernosus* which occurs reflexly as the urine enters the initial portion of the urethra.

Micturition is a typical reflex process. The lower level on which the reflex arc of this reflex closes is the 2nd, 3rd and 4th sacral segments of the spinal cord where the cell bodies of the efferent neurons of the bladder muscles are located and the afferent fibres of its receptors enter. The spinal neurons of the micturition centre are controlled by the higher division of the central nervous system—the cerebral cortex. Cortical influences make possible "voluntary" retention of the urine or, on the contrary, "voluntary" micturition.

Regulation of micturition involves the cerebral cortex. Airapetyants demonstrated in his experiments the possibility of influencing micturition by conditioned reflexes. Increased pressure is produced in the urinary bladder of the person studied by an ingestion of water into the bladder through a catheter. The muscles of the bladder contract and a desire to micturate is experienced when the distention of the bladder and the pressure reach a certain stage which is registered by a manometer (Fig. 168).

The subject continuously watches the manometer. The constant combination of the micturition reflex with the signal—reading on the manometer, which indicates the value of the pressure in the bladder, leads to the development of a conditioned reflex. Micturition occurs when the subject sees a certain pressure value on the manometer. Moreover, the pressure figure shown on the manometer causes micturition even when the manometer is disconnected from the bladder and no liquid has really been ingested into it (the pressure in the bladder is close to zero). Contrariwise, if no rise in pressure signalizing the distention of the urinary bladder is registered by the manometer the bladder may be filled with 400, 500 or 600 ml. of liquid, the pressure may be raised to twice the value which usually causes micturition and the subject will manifest no signs of reaction to the increased pressure in the bladder. An uttered word designating stimuli, which usually cause micturition, leads to a rise in pressure in the urinary bladder and to micturition with no real distention of the bladder. The signals which the activity of the cerebral cortex associates with the state of the urinary bladder may replace, as it were, the impulses from its interoceptors. Under normal conditions micturition is in large measure determined by conditioned reflexes produced to situations in which this act is usually performed; this leads to difficulties when it is necessary to perform it under other circumstances, for example, lying on a bed-pan, etc.

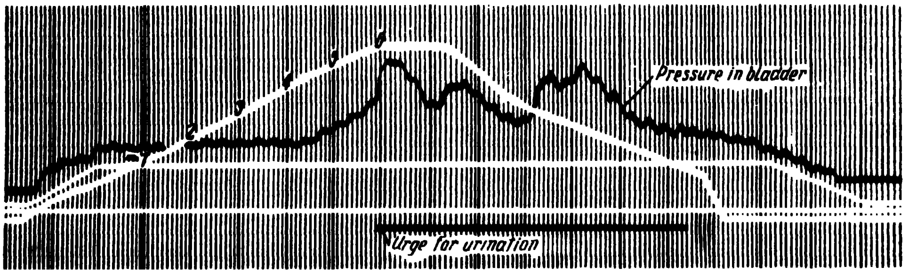


Fig. 169. Rise in pressure in urinary bladder, appearance of urge for urination and change in skin potentials in response to oral signal of distention of the urinary bladder—uttering figures 1, 2, 3, etc. (shown on wide white band), designating such rise in pressure in the manometer which in former experiments on given person took place when liquid was infused into urinary bladder (after E. Airapetyants).

Extrarenal Excretory Processes

The kidneys are the main, but not the only organ through which the processes of excretion take place. The significance of excretion of faeces has already been dealt with. The skin, liver and lungs are also excretory organs.

Excretory function of skin. In addition to protecting all the underlying tissues, the skin also discharges another function, that of eliminating a number of compounds with the sweat. The most important part played by the skin is that of excreting water; this process is significant not only from the point of view of excretion, but also as a most important mechanism of thermoregulation. We must remember that in addition to water, salts (chiefly chlorides), lactic acid and products of nitrogenous metabolism are also excreted with perspiration. In profuse perspiration this is of essential importance. Elimination of urea and other compounds through the skin may to some extent compensate for a deficiency in the functions of the kidneys.

Even outside the process of perspiration the skin is capable of retaining considerable amounts of water and sodium chloride. If large quantities of water and common salt are consumed their content in the skin markedly increases and remains on a high level for a rather long time. The reaction of the skin, especially its surface layers, is acid which, probably, attenuates bacteria.

Excretory function of liver and lungs. The importance of bile production to the processes of excretion is apparent from the fact that the inability to eliminate the bile, which is manifest in jaundice, leads to serious consequences and sometimes even to death. The products of haemoglobin dissociation (bile pigments) and the cholesterol derivatives (bile acids) are excreted with the bile. Part of these products is reabsorbed in the intestines into the blood, undergoes additional changes and is excreted by the kidneys or eliminated with the faeces so that the liver is not an organ whose *direct* function is excretion. The role of the liver in excretion is inseparable from its role in all processes of intermediate metabolism.

Water vapours which saturate the expired air are always eliminated with it in quantities varying with pulmonary ventilation and the humidity of the inspired air. Some authors believe that negligible quantities of some poisonous substances are eliminated with the expired air, but this has not found any confirmation as yet.

PART X

PHYSIOLOGY OF THE ENDOCRINE GLANDS

CHAPTER 39

METHODS OF INVESTIGATING THE FUNCTIONS OF THE ENDOCRINE GLANDS

The products of metabolism which come into the blood from the tissues and are carried by the blood throughout the organism produce a definite physiological action. For example, the CO_2 of the blood exerts a marked influence on the central nervous system and is one of the important agents in the regulation of the respiratory movements (see Chapter 21). Apart from the nonspecific metabolites common to many tissues, certain specific substances are secreted into the blood by special organs having a special histological structure; these substances produce a considerable physiological effect upon the metabolic processes and upon the course of various physiological functions.

The secretion of specific substances directly into the blood, unlike the external secretion, which from the glands passes through ducts onto the surface of the body, or into certain cavities (alimentary canal, respiratory tracts, etc.), is designated as *internal secretion*. The organs which produce such substances are called *glands of internal secretion*, or *endocrine glands*. The physiologically active substances elaborated by the endocrine glands and secreted into the blood are termed *hormones*. The endocrine activity is also called *incretory*.

The century-old experience of mankind in the field of animal husbandry led already in ancient times to the practice of castration (removal of the sex glands) for the purpose of fattening animals, or of using them as draught animals. The connection between castration and modifications of the secondary sexual characters in man was also known long ago. But the role played in the development of the secondary sexual characters by the introduction of the products of the sex glands into the blood (Berthold's experiments with engrafting in castrated cocks of testes previously excised from them, 1849) was clearly conceived only in the middle of the 19th century. The development of the theory of internal secretion owes much to Claude Bernard who was the first to suggest the very term "internal secretion." The experiments of Brown-Séquard (1889) who injected testicular extracts of animals into himself produced a great impression: the injections brought about a marked improvement in the physical state and working capacity of the aged scientist who was 72 years old at the time. Although this effect, as it turned out later, was a result of autosuggestion, Brown-Séquard's experiments attracted wide attention to the problems of internal secretion.

Observations of patients suffering from the bronzed disease (Addison's disease) led to the conclusion that an important role was played by the adrenals. Surgical operations in the region of the thyroid gland and observations of patients suffering from Basedow's disease and myxoedema provided sufficient data to determine the role of the thyroid secretion. The study of diseases caused by metabolic disorders and the experiments aimed at reproducing these disorders in animals, made it possible to establish the endocrine function of the islands of Langerhans, the function of the parathyroid glands and the hypophysis. The term "hormone" was introduced by Bayliss and Starling at the beginning of this century in connection with their discovery of secretin (page 281).

Experimental investigations of the endocrine glands in laboratory animals are based on observations of the consequences produced by extirpation of these glands, and of the effects of the introduction into the organism of the active products secreted by the glands. In the main these methods of investigation correspond to the experiments performed in all branches of physiology, namely, the extirpation and stimulation of certain organs.

The surgical removal of a gland terminates the passage of its hormones into the blood. The concomitant disturbances of metabolism and of the growth and development of the organism are due to the exclusion of this gland. The deficiency in the corresponding hormones can be made up either by transplanting similar glands from another animal or by introducing their extracts into the organism.

Since certain hormones are destroyed in the gastrointestinal tract, the action of glandular extracts upon the organism must be studied with the aid of parenteral administration. Such experiments are most frequently performed on animals in which the corresponding gland has been removed; in these cases the administration of extracts from the missing gland or of its preparations containing active hormones clearly prevents or eliminates the disorders caused by the removal of this gland. But hormones introduced into the blood also affect normal animals because their action is added to that of the hormone produced by the corresponding gland.

In order to establish the chemical nature of the hormones, the substances of which the extracts or products of decomposition of the glandular tissue consist are isolated and the physiological action of each of the products thus obtained is tested. A chemically pure substance with a specific action, i.e., a pure hormone, is finally produced. If the chemical structure of the hormone is not very complex, its study usually results in a chemical synthesis. Similar effect of a product obtained synthetically and of that obtained from a gland is the final proof of the chemical nature of the hormone under investigation.

Human pathology shows that certain glands are affected by various diseases (tuberculosis, tumours, etc.). Disorders of glandular activity, the nature of which is not clear as yet and in which either less hormones (hypofunction) or more hormones (hyperfunction) are produced, are also observed. Sometimes the function of the endocrine glands is impaired, i.e., there is a dysfunction of the endocrine glands. In some cases, because of a lesion, an endocrine gland is surgically either fully or partially removed. All disturbances of metabolism, growth, development, working capacity, etc., observed in the aforesaid cases, make it possible to evaluate the significance of the various endocrine glands.

Anatomo-physiological features common to the endocrine glands. As a rule, the endocrine glands are small organs. Except the thyroid gland, which weighs from 40 to 50 gr., the weight of any endocrine gland does not exceed several grams and often constitutes only a fraction of a gram.

The total lumen of the arteries which supply these organs with blood is considerably larger than could be expected judging by the size of the endocrine glands. The arteries are divided into a dense capillary network ensuring a rich supply of blood to the endocrine glands. In the hypophysis the structure of the vascular system bears the character of a portal system. The superior hypophyseal artery breaks up into a vascular plexus which entangles the stalk of the hypophysis and of *pars tuberalis*. Then the vessels of this plexus unite into blood sinuses of the anterior lobe of the hypophysis; from the latter the blood passes along the veins into the *sinus cavernosus*.

The abundant vascularization of the endocrine glands is undoubtedly connected with the nature of the physiological function of these glands, i.e., the substances produced by them should easily pass into the blood. Since there are many substances with a considerable molecular weight among the hormones (some hormones of a protein nature) or substances of low solubility (hormones of a steroid nature), their passage into the blood stream requires a large surface of contact between the cells of the endocrine glands and the walls of the blood vessels.

The endocrine glands are supplied both with vasomotor nerves and nerves which act upon the glandular tissue. The nerve fibres in the endocrine glands are unmyelinated and belong to the vegetative nervous system. The tissue of the thyroid gland is supplied with sympathetic fibres of the superior cervical sympathetic ganglion and with parasympathetic fibres (vagus nerve). The hypophysis is innervated from the superior sympathetic ganglion and from the nuclei of the hypothalamic region. The medullar substance of the adrenals is innervated by sympathetic fibres of the splanchnic nerve. In the pancreas the islands of Langerhans, which discharge an endocrine function, are innervated by nerve fibres (mainly of the vagus) differing from the fibres which supply nerve endings to the exocrine elements of the gland.

Since the activity of the endocrine glands is stimulated by nerves, their function is controlled by the central nervous system and is integrated with it. Agents of the external and internal environment influence the production of hormones through the central nervous system. Introduced into the blood and carried by it throughout the organism the hormones act upon corresponding physiological systems and organs.

CHAPTER 40

INTERNAL SECRETION OF THE THYROID AND THE PARATHYROIDS

In the course of embryonic life the thyroid develops from rudiments which bulge out from the ventral part of the foregut. In the adult the gland consists of two oval bodies lying on either side of the lower part of the larynx and trachea and joined by an isthmus. The gland is made up of follicles which represent cavities lined by a layer of cubical epithelial cells and filled with "colloid"—a semiliquid viscous mass. The follicles are separated from one another by layers of connective tissue. The products of secretion are poured into the blood. The thyroid is richly supplied with blood by three arteries. It receives three times its own weight of blood per minute. Before the secretory function of this gland was learned it had been regarded as a regulator of blood circulation.

The thyroid contains abundant unmyelinated nerve fibres running from the superior cervical sympathetic ganglion and parasympathetic nerve fibres from the vagus. The nervous system controls the work of the thyroid through these fibres.

Hypothyroidism and Hyperthyroidism

It has long been known that inhabitants of certain localities have enlarged thyroids. These people develop a goitre (a swelling in the front part of the neck), owing to which the disease itself is called *endemic goitre* (the word "endemic" signifying that this disease is peculiar to a certain locality). The function of the thyroid is sharply reduced (hypothyroidism) due to the degeneration of its glandular tissue. The disease is accompanied by lowered metabolism, a slow pulse, dry and wrinkled skin, mucous oedema, apathy and mental deficiency. The disease has been named myxoedema (which means mucous oedema). Its development is due to an accumulation of mucin in the intercellular fluid; the colloid-osmotic pressure rises and leads to retention of water.

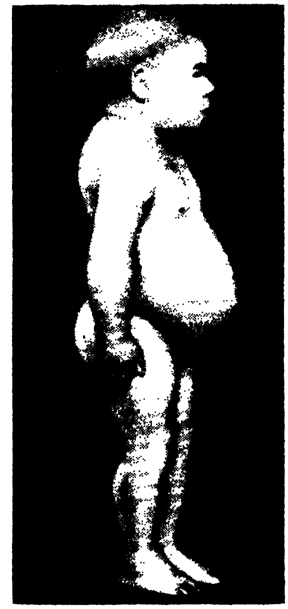


Fig. 170. Eighteen-year-old patient afflicted with myxoedema and cretinism (after N. Shereshevsky).

Cases of *cretinism* are frequent in localities where endemic goitre is widespread; this condition is marked by arrested physical and mental development, dystrophy of the skeleton, underdevelopment of the sex glands, coarseness of the skin, weakness of the memory, inability to think abstractly, etc. The disease is caused by failure of the thyroid to develop congenitally or in childhood. The earlier it occurs the more retarded the physical and mental development (Fig. 170).

Extirpation of goitres in children attempted in the eighties of last century (Kocher) only further impaired the health of the patients. Experiments in which the thyroid in animals is excised reproduce in general outline the picture of thyroid deficiency in man: the metabolism drops, the pulse slows down, the skin becomes dry and oedematous and the hair falls out. The animal becomes dull, sluggish and indifferent to the surroundings. Young animals subjected to this operation fail to grow (Fig. 171).

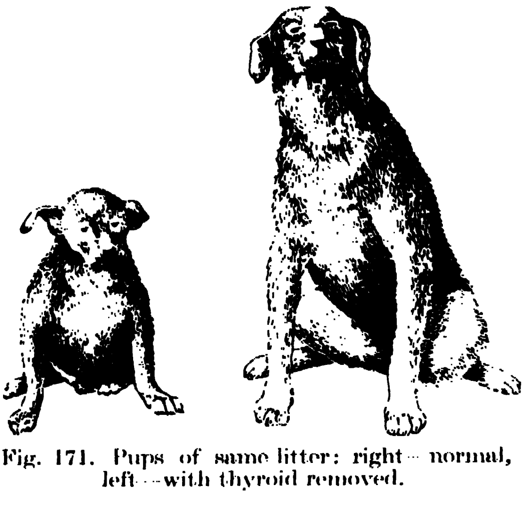


Fig. 171. Pups of same litter: right — normal, left — with thyroid removed.

Removal of the thyroid at early stages of development in lower vertebrates impedes their metamorphosis. For example, excision of the thyroid in tadpoles prevents their development into frogs.

Another disorder of the thyroid is its excessive function or hyperthyroidism. This disturbance is also accompanied by an enlargement of the gland, though it is not so pronounced as in severe forms of endemic goitre. In this case, however, the tissue of the gland produces more hormone than in the healthy individual. This disease was described as far back as the first half of the 19th century by Graves and subsequently by Basedow and is called Basedow's disease. Investigations of patients suffering from this disease disclose the following three symptoms: enlargement of the thyroid gland, protrusion of the eyeballs (exophthalmos, Fig. 172) and accelerated heart rate. Other essential symptoms are: increased metabolism, rise in body temperature and muscular weakness.

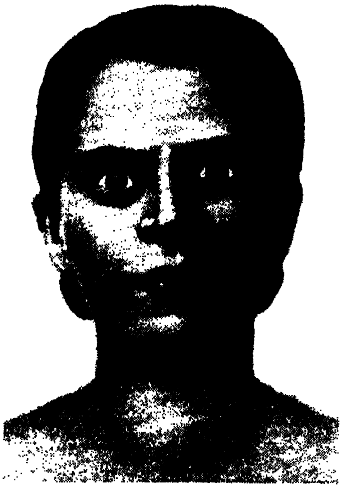
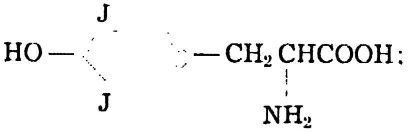


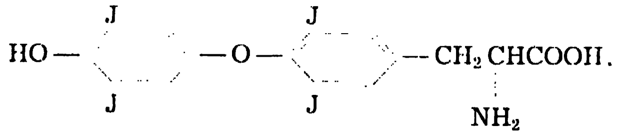
Fig. 172. Patient with Basedow's disease.

Hormone of the Thyroid

Thyroid deficiency is successfully treated by addition of fresh thyroid tissue of animals or its dry preparations to the food. One of the proteins of the thyroid, *thyroglobulin*, contains iodine. Alkaline hydrolysis of this substance produces simpler iodine-containing substances, namely, *diiodotyrosine* and *thyroxin*.



Diiodotyrosine



Thyroxin

These substances were subsequently also obtained synthetically. The active principle of the thyroid gland is thyroxin.

Thyroxin, when introduced subcutaneously, raises general and protein metabolism, decreases the ability of the liver to store glycogen, increases the excretion of urine and, together with it, of nitrogenous products, raises the excitability of the nervous system and accelerates the heart rate. Administered to patients suffering from thyroid deficiency it produces a therapeutic effect removing the symptoms of hypothyroidism.

Administered in large quantities to lizards and birds thyroxin and the preparations of the thyroid provoke premature moulting; hens may moult so rapidly as to lose all their feathers within several days (B. Zavadovsky). In tadpoles thyroxin and thyroid tissue accelerate metamorphosis; before attaining their full size the tadpoles turn into small frogs.

Thyroxin is a strongly acting substance. Already in a dilution of $1:10^8$ it clearly influences the metamorphosis of tadpoles. Administration of

10 mg. of thyroxin to a myxoedema patient produces a considerable rise in the gaseous exchange lasting many days (Fig. 173).

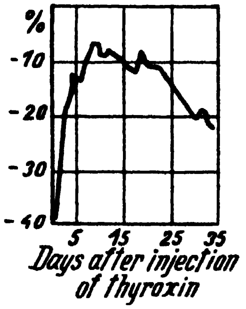


Fig. 173. Curve shows changes in general metabolism of adult male, suffering from myxoedema, after intravenous injection of 10 mg. of thyroxin.

Along ordinate deviations in metabolic rate from normal in % (after Boothby and Gauntry).

The human body contains little thyroxin—about 20 mg. Experiments with radio-active iodine have revealed that thyroxin is rapidly synthesized in the thyroid gland. Iodine, administered as potassium iodide subcutaneously, is retained mainly in the thyroid as diiodotyrosine and thyroxin.

Thus, the normal functioning of the thyroid requires an adequate supply of iodine. Man daily requires 0.15 to 0.3 mg. of iodine, while the human blood contains only 0.003 to 0.01 mg. per cent of it. Most of the iodine required comes to the human organism with drinking water and vegetables, and endemic goitre is widespread where the ground and drinking water contain too little iodine. The lack of iodine in drinking water can be made up by the addition of requisite quantities of potassium iodide to the common salt (1 gr. KJ per 100 kg. NaCl).

Diiodotyrosine and thyroxin can be produced *in vitro* by iodizing proteins in the presence of hydrogen peroxide. Some reducing agents, such as thiourea and a number of its derivatives, prevent the formation of thyroxin *in vitro* and *in vivo*. Administration of some derivatives of thiourea (for example, thiouracil) is very effective in Basedow's disease because it reduces the synthesis of thyroxin in the patient's thyroid gland.

Thiouracil inhibits the synthesis of thyroxin, but does not neutralize the thyroxin which has already entered the blood. Unlike thiouracil paraxanthine (1.7 dimethylxanthine), one of the derivatives of purine, is an antagonist of thyroxin and decreases metabolism.

Regulation of Thyroid Activity

Thyroid activity is controlled by the nervous system, the influence of the latter being effected directly through the nerve fibres running to the thyroid and through other endocrine glands (hypophysis, sex glands).

The role of the cerebral cortex in supplying thyroxin to the blood was established by R. Olnyanskaya who succeeded in elaborating a conditioned-reflex increase of metabolism, apparently due to the passage of thyroxin from the thyroid to the blood. The significance of the sympathetic nerve fibres was demonstrated by the experiments of W. Cannon and by those of A. Tonkikh, in L. Orbeli's laboratory. If the peripheral end of the sympathetic nerve running to the gland from the superior cervical sympathetic ganglion is sutured to the distal end of the phrenic nerve, the animal develops hyperthyroidism accompanied by increased metabolism, acceleration of the pulse, etc. It is probable that as soon as the fibres of the phrenic nerve reach the tissue of the gland the rhythmic excitation of the nervous centres from which this nerve issues provokes a constant flow of impulses to the gland, and this in its turn induces the gland to synthesize the incretion.

The regulation of thyroid function is also effected through the hypophysis. The anterior lobe of the hypophysis elaborates a thyrotropic hormone, i.e., a hormone which intensifies the function of the thyroid.

Activity of the Parathyroids

The parathyroids are four small oval-shaped bodies; in man they are located in the capsule of the thyroid at its lateral edges; in some animals (for instance, in rabbits) they lie outside the thyroid gland. Each human parathyroid weighs about 0.1 gr. The parathyroids develop from the protrusions of the third and fourth branchial arches and in a developed state represent thick columns of epithelial cells (hence, the parathyroids are also called *epithelial bodies*) surrounded by connective tissue and richly vascularized.

Removal of all parathyroids in animals soon causes spasms (*tetany*) and death. Before the physiological role of the parathyroids was known they were sometimes inadvertently removed in thyroidectomies with the same fatal results.

Spasms caused by removal of the parathyroids or their hypofunction are due to a sharp increase in the excitability of the neuromuscular system. The galvanic excitability of the motor nerves is increased. A light tap on the face in the region of the facial nerve causes the facial muscles to contract (Chvostek's sign). Pressure on the upper arm with a sphygmomanometer cuff may produce carpal spasm. In a spasm the hand assumes a characteristic position known as the "obstetrician's hand" (Fig. 174). Since the posterior muscles of the neck are much stronger than the anterior muscles, the head is drawn back (opisthotonos). The spasm may also spread to the muscles of the internal organs—the pylorus (pylorospasm) and the larynx (laryngospasm). During pylorospasm food fails to pass from the stomach into the duodenum and uncontrollable vomiting results. Laryngospasm is especially dangerous since it may lead to suffocation.

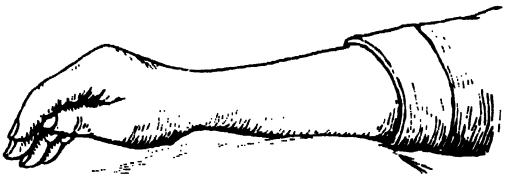


Fig. 174. "Obstetrician's hand" during tetanic attack due to deficiency of parathyroids.

Tetany caused by dysfunction of the parathyroids may result from traumas to these glands, certain infectious diseases and poisoning (by phosphorus and lead). Tetany not infrequently occurs in children in the first or second year of life (spasmophilia).

Modifications in the state of the neuromuscular system are due mainly to changes in the calcium content of the blood plasma. Lack of the parathyroid hormone in the blood reduces the blood calcium from between 9 and 12 to 5 or 7 mg. per cent. The mechanism by which the blood calcium content is reduced is, apparently, as follows: lack of the parathyroid hormone raises the threshold for the excretion of phosphates by the kidneys. The excretion of phosphates with the urine decreases, and the phosphate content in the blood plasma increases. The very low solubility of calcium phosphate reduces the calcium content. Introduction of calcium salt into the blood lowers the excitability of the neuromuscular system, but this effect does not last long; the calcium is rapidly eliminated from the blood, and conditions are again created for the recurrence of spasms. Apart from changing the blood calcium content the parathyroid dysfunction shifts the acid-base balance of the organism towards an alkaline excess (alkalosis) and an accumulation of guanidine bodies in the organism.

Administration of the parathyroid hormone increases the elimination of phosphates with the urine, decreases the content of phosphates in the blood plasma, and results in a strongly pronounced (up to 20 mg. per cent) and protracted increase in blood calcium.

The parathyroid hormone is a protein body. It is easily destroyed by proteolytic enzymes and therefore cannot be administered by mouth.

Some tumours and hyperplasia of the parathyroids are responsible for an excess production of the parathyroid hormone which is accompanied by an increase in the calcium content, a drop in the content of inorganic phosphates of the blood plasma, an accumulation of calcium salts in many organs (lungs, liver, kidneys, skin, large blood vessels, endocrine glands, etc.), diseases of the skeletal system (increased porosity and excess growth of fibrous tissue) and the muscles (reduced efficiency).

CHAPTER 41

INTERNAL SECRETION OF THE PANCREAS

Islands of Langerhans

Clusters of cells (in man each cell is several tenths of a millimetre in size) which have no communication with the ducts of the gland are dispersed like islands in the glandular tissue of the pancreas. These so-called islands of Langerhans are richly supplied with blood vessels, owing to which the products elaborated in these cells easily get into the blood stream.

At the end of the 19th century it was found that extirpation of the pancreas resulted in diabetes mellitus (increase in the blood sugar, appearance of sugar in the urine, disturbance of carbohydrate and fat metabolism—see p. 315). Subcutaneous grafting of the pancreas in such animals removed the disturbances in carbohydrate metabolism. In 1900, L. Sobolev found that after ligature of the pancreatic ducts the glandular tissue atrophied, while the islands remained intact. On the contrary, in people suffering from diabetes the island tissue degenerates and sometimes disappears entirely. Changes in the island tissue are the more pronounced, the greater the disturbance of carbohydrate metabolism in the patient before his death. Hence, Sobolev concluded that the islands of Langerhans were "blood glands" (i.e., glands of internal secretion) indispensable to the regulation of carbohydrate metabolism. He also outlined methods of treating diabetes. It was known that the use of the entire pancreas in the treatment of diabetes failed since it was rich in trypsin (an enzyme which destroys the active principle entering the blood). Sobolev proposed to utilize the pancreatic glands whose tissues atrophy after ligature of the duct, or pancreatic glands of newborn animals (for example, calves) in which the island tissue is already well developed, while the cellular elements producing the enzymes of the pancreatic juice are still inadequately represented.

Twenty-two years later this method suggested by Sobolev was further developed by two Canadian scientists Banting and Best for obtaining *insulin* (insula means island), the hormone produced by the islands.

Insulin and Its Action

Insulin, the hormone of the island tissue, is a protein with a molecular weight of 12,000. A molecule of insulin consists of four polypeptide chains, in which the amino acid composition and the succession of the amino acids is almost fully known (Saenger). Insulin preparations usually contain zinc; pure insulin preparations containing no zinc can be obtained, however, without reducing the effectiveness of the insulin.

As a protein substance insulin is easily destroyed by proteolytic enzymes. This is why in the past researchers failed to obtain the active principle of the island tissue through mincing the tissue of the pancreas with subsequent extraction by water solutions. In this procedure the proteolytic enzymes contained in the pancreas rapidly destroyed the insulin. In preparing insulin today the cooled pancreas is rapidly minced in a cold mixture of water and alcohol acidified by hydrochloric acid. Under these conditions the proteolytic enzymes are rapidly inactivated. Since insulin is easily destroyed by proteolytic enzymes, it cannot be administered by mouth and must be introduced subcutaneously or intravenously.

When insulin is introduced into the blood the content of blood sugar decreases, the decrease varying with the amount of insulin entering the blood. Thus, hyperglycemia observed in diabetes can be relieved and the passage of sugar into the urine, i.e., glycosuria, can be stopped.

The changes in metabolism underlying hypoglycemia have not yet been sufficiently elucidated. When insulin is injected an increase in the synthesis of glycogen and in the oxidation of carbohydrates is observed.

Excessive introduction of insulin into the blood drives the blood sugar content below the normal limit. This condition is designated as hypoglycemia. The latter may become so acute as to derange the supply of glucose to the brain. The animal develops hypoglycemic shock expressed in convulsions and coma. The shock is rapidly relieved by introduction of glucose into the blood which proves that hypoglycemic shock is caused mainly by a low content of sugar in the blood. When large quantities of insulin are administered it acts for many hours. A single administration of glucose therefore maintains a high sugar concentration but a short time, and hypoglycemic convulsions may recur necessitating repeated administration of glucose. Failure to administer glucose during a severe hypoglycemic shock in due time may lead to death.

It follows that as a remedy insulin must be used sparingly, at the discretion of a physician and in doses strictly corresponding to the needs of the disease.

Insulin is a protein body and we therefore have no chemical methods of estimating its quantity in the presence of other proteins. Since insulin preparations differ, their dosage must be based on a knowledge of the physiological action of each preparation. The accepted "unit of action" is one-third of the amount required to reduce the content of blood sugar to 45 mg. per cent in a two-kg. rabbit after 24 hours of fasting. Standard preparations contain about 8 units per 1 mg. of dry substance. In view of the rapid destruction of insulin in the tissues it must be administered to diabetic patients several times per day, the daily dose usually constituting 20 to 40 and even up to 100 units

Regulation of Insulin Secretion

The ability of the island tissue to produce insulin is retained even when the pancreas is fully denervated, or transplanted subcutaneously. The finer regulation, however, is effected by the nervous system. It has been found that the secretion of insulin is stimulated by the vagus.

The natural and constant factor which influences the secretion of insulin in a healthy individual is the content of blood sugar. With a high concentration of blood sugar greater amounts of insulin enter the blood and the sugar content decreases as a result. This is revealed by the study of the so-called "sugar curves" which reflect the changes in the content of blood sugar at different intervals after the intake of large quantities of sugar. An increase in the content of sugar, as a result of its absorption, is often followed by its sharp decrease, even below the normal limit. With a low concentration of blood sugar the secretion of insulin is retarded and is accompanied by an increase in the content of sugar in the blood. This is why a rapid decrease in the blood sugar is often followed by a second, though shorter, rise in the "sugar curves." It should not be forgotten that in addition to insulin the blood sugar is also influenced by adrenalin (a hormone of the adrenal medulla): passage of the latter into the blood leads to an increase in the blood sugar content, i.e., produces an effect contrary to the action of insulin.

The blood sugar influences the secretion of insulin to a certain extent directly through sugar-rich blood flowing to the cells of the island tissue. There is apparently another, more essential way, however. It has been demonstrated that if blood having a high sugar content is perfused through the blood vessels of a head connected with the body only by the vagi, the supply of insulin into the blood increases.

In diabetes hyperglycemia does not exert any influence on the island apparatus because of its atrophy or hypofunction. The island apparatus can be degenerated experimentally by the introduction of alloxan which affects the cells of the island tissue selectively. Thus it is possible to develop diabetes in animals (alloxan diabetes).

Lipocaic Substance of the Pancreas

In addition to insulin, the tissues of the pancreas contain a substance the deficiency of which leads to fatty degeneration of the liver and a decrease in the lipoid content of the blood. Administration of insulin does not remove these disturbances and animals in which the pancreas has been extirpated die within two or three months even if they are regularly given requisite amounts of insulin. The death of such animals can be averted only if they are fed a definite amount of pancreatic tissue of other animals.

Fatty degeneration of the liver is also caused by lack of choline and methionine. These substances are contained in the tissue of the pancreas, but the function of the latter cannot be confined exclusively to the production of these substances and it is therefore supposed that some other specific substance is elaborated in the pancreas.

This, yet insufficiently known substance contained in the pancreas and indispensable to the regulation of lipoid metabolism has been termed *lipocaic substance.* There is no doubt that some forms of diabetes are complicated due to an insufficient supply of the lipocaic substance to the organism.

CHAPTER 42

INTERNAL SECRETION OF THE ADRENALS

The Adrenal Cortex and the Adrenal Medulla

The adrenals are two small bodies (each weighing from 5 to 8 gr.) situated near the upper pole of the kidneys. As regards phylogenetic origin and embryonic development each adrenal represents two different organs which in higher animals are anatomically united forming a single whole.

The central part of this organ is the medulla which is formed from the *adrenal* tissue. It consists of cells of the sympathetic nervous system and of cells containing granules coloured brown by chromic acid and green by salts of iron. Hence they are designated as *chromaffin* cells. Adrenal tissue can be found also outside the adrenals in the form of small knots.

The outer part of the adrenals or their cortex is formed by the *interrenal* tissue. The cells of this tissue contain numerous granules of a lipoid nature.

In fishes the adrenal and interrenal tissues are anatomically separated. Beginning with amphibians and ending with mammals, these tissues grow into each other and form a single organ.

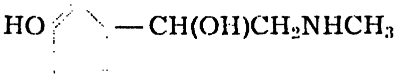
In the course of embryonic development the chromaffin tissue is formed from the same ectodermal cells as the sympathetic nervous system. The interrenal tissue is of a mesodermal origin, common with that of the sex glands.

Physiologically both tissues perform the functions of endocrine glands. However, they have separate systems of blood circulation and produce incretions which differ both in their chemical nature and physiological effect.

The adrenals are richly supplied with blood: they receive seven times their own weight of blood per minute.

Hormone of the Adrenal Medulla

The adrenal medulla secretes *adrenalin* (its other names are *epinephrine* and *suprarenin*). Chemically it represents the 1-form of methylaminoethanolpyrocatechol. For therapeutic purposes adrenalin is produced synthetically.



Adrenalin

The physiological action of adrenalin coincides with the effect produced by the excitation of the sympathetic nervous system (*sympathomimetic action*). Thus the hormone accelerates the heart rate, intensifies cardiac contractions and constricts the small arteries and arterioles. The blood vessels of the heart and brain are an exception: under the influence of adrenalin they dilate. Adrenalin raises the blood pressure, slows down the contractions of the smooth muscles of the intestinal tract and reduces its tone. It causes the pupil to dilate by a contraction of its muscle. The secretion of the mucous glands in the oral cavity and in the respiratory tracts increases, while that of the sudoriferous glands diminishes in most animals. The working capacity of the muscles increases.

Adrenalin exerts a marked influence on carbohydrate metabolism. The liver glycogen breaks up and forms sugar owing to which the content of sugar in the blood increases. Not only the formation of sugar in the liver, but also its consumption in the tissues is intensified. General metabolism and heat production increase.

Minute amounts of adrenalin (0.01 mg. and less per kg. of body weight) injected into the organism suffice to produce all the aforesaid effects. The blood normally contains very little adrenalin ($1:10^8$ to $1:10^9$). There is less adrenalin in the systemic circulation than in the venous blood, which flows away from the adrenals and in the blood of the pulmonary circulation. This is due to its instability. It easily oxidizes under a weak alkaline reaction in the presence of oxygen and yields several oxides. Therefore, even during the short interval between the passage of adrenalin from the adrenals into the venous blood and the entrance of this portion into the arteries a considerable part of the adrenalin becomes oxidized.

In addition to adrenalin the adrenals contain another substance which is close to adrenalin and which acts on the heart and blood vessels in a similar way; it is *noradrenalin* (arterenol)—a demethylated adrenalin.

Regulation of adrenalin secretion. The adrenal medulla is innervated by sympathetic fibres which form part of the splanchnic nerves. M. Cheboksarov in N. Mislavsky's laboratory and subsequently V. Savich found that stimulation of the peripheral end of the splanchnic nerve greatly increased the secretion of adrenalin. Contrariwise, a transection of the splanchnic nerve discontinues the secretion of adrenalin. This secretion can also be provoked by stimulation of the floor of the IV ventricle. The secretory activity of the adrenal medulla no doubt also depends on the state of the cerebral cortex. Pain stimulations or emotional excitation increase the supply of adrenalin to the blood. For example, if the cat becomes excited in the presence of the dog, several phenomena (dilation of the pupils, acceleration of the heart-beat, erection of the hair) testify to the passage of adrenalin into the blood; indeed, blood taken from the vena cava of this cat contains more adrenalin (Cannon). Substances acting on the sympathetic system, such as nicotine taken in definite doses, augment the secretion of adrenalin. One of the substances greatly stimulating the secretion of adrenalin is adrenalin itself. This is due to the fact that adrenalin exerts an excitatory influence on the sympathetic nervous system, including the splanchnic nerve which innervates the adrenals.

Activity of the Adrenal Cortex

Removal of both adrenals in an animal kills the animal within a few days after the operation, the interval depending on the species of the animal, its state and conditions under which it is kept. The death of the animal is preceded by a strongly pronounced and progressive state of muscular weakness (*muscular adynamia*). Administration of an adrenocortical extract augments the efficiency of the muscular apparatus of the animal and averts its death. Removal of the adrenal medulla alone produces no grave consequences. Thus, it is not the secretion of the medulla which constitutes the vitally important activity of the adrenals, but rather their cortical substance.

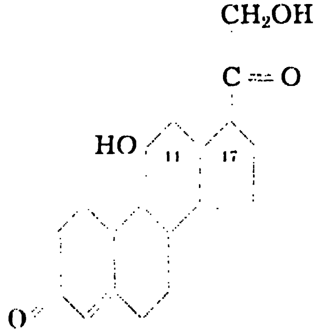
Adrenocortical insufficiency is responsible for disorders of many functions and metabolic processes. The general symptoms include extreme muscular weakness, sometimes vomiting and diarrhoea and loss of appetite. The processes of sugar and fat absorption in the intestines are deranged, the heart rate is accelerated and the blood pressure drops. Less urine is excreted and the content of nitrogenous products of protein metabolism (residual nitrogen, urea) increases. Thermoregulation is disturbed and body temperature is lowered. The acid-base balance shifts in the direction of acidosis (decrease in the pH and in reserve alkalinity).

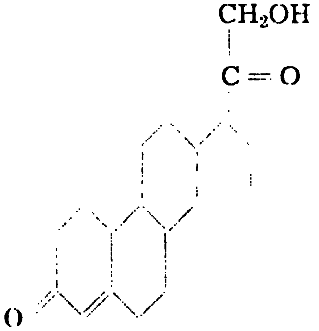
Derangements in the sodium and potassium metabolism, however, are chiefly responsible for the disorders of metabolic processes. Removal of the adrenals increases the excretion of sodium and chlorides with the urine which considerably reduces the content of sodium and chlorides in the blood plasma. Contrariwise, the content of potassium in the plasma increases owing to its slower excretion with the urine. Under these conditions passage of potassium into the blood may prove fatal; an increase of potassium in the blood plasma to about 60 mg. per cent is toxic. Since ordinary food is rich in potassium and poor in sodium, its consumption markedly aggravates the condition of an adrenalectomized animal. If, on the contrary, such an animal is given potassium-poor food with an addition of sodium salts the animal can be kept alive for a long time.

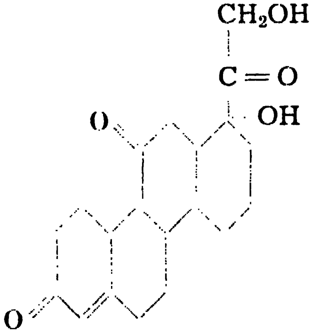
In man dysfunction of the adrenal cortex complicated by other phenomena is observed in tuberculosis of the adrenals characterized by muscular adynamia and a dark pigmentation of the skin; the disease is therefore called *bronzed disease* or Addison's disease, after the British physician who was the first to describe it.

Hormones of the Adrenal Cortex

The adrenal cortex elaborates more than twenty different, physiologically active substances of a steroid nature, which are designated as cortical hormones. Of these hormones corticosterone was the first to be obtained in a pure form. It is able partly to remove the symptoms of adrenocortical insufficiency. One of its derivatives—11-desoxycorticosterone (C_{11} has no atom of oxygen)—strongly influences sodium and water metabolism (it retains sodium and water in the organism). Some other derivatives of corticosterone (11-desoxy-17-oxycorticosterone, 11-dehydro-17-oxycorticosterone, or cortisone, and others) increase carbohydrate and protein metabolism. These hormones improve sugar absorption from the intestines, stimulate


Corticosterone


11-desoxycortico-sterone


11-dehydro-17-oxycorticosterone (cortisone)

formation of glucose at the expense of proteins and increase muscular strength. Cortisone (11-dehydro-17-oxycorticosterone) is also efficacious against some articular diseases (rheumatoid arthritis). In addition, the cortical hormones may to a certain extent act like the sex hormones. One of the adrenal dysfunctions in females is expressed in *adrenal virilism*, marked by a development of certain male secondary sex characters (growth of hair on the face, deep voice) and a discontinuance of menstruation. In children disturbances in adrenal activity may lead to premature sexual development.

CHAPTER 43

INTERNAL SECRETION OF THE HYPOPHYSIS, EPIPHYSIS AND OTHER GLANDS

Structure of the Hypophysis

The hypophysis, or pituitary gland, is situated above the base of the brain and is connected with the latter by a funnel infundibulum) which passes into a stalk. In man this organ weighs from 0.5 to 0.7 gr. Despite its small size, the hypophysis has a very complex structure and an extremely varied secretory activity.

The hypophysis consists of four parts: the anterior lobe, posterior lobe, ***pars intermedia*** and ***pars tuberalis*** (Fig. 175). The anterior lobe is called glandular. In the course of embryonic development it arises from the buccal epithelium. It consists of epithelial cells which are differently stained by basic and acid colours (acidophilic, basophilic and chromophobic cells). The endocrine activity of the anterior lobe of the hypophysis is particularly diverse. The posterior lobe of the hypophysis or its nervous part consists of spindle-shaped cells and cells of neurogliar tissue. It develops from the central outgrowth of the cerebral vesicle. ***Pars intermedia*** is a narrow strip consisting of epithelial cells. In front it is separated from the anterior lobe by a cleft which is a vestige of the embryonic hollow outgrowth. Posteriorly it closely adjoins ***pars nervosa***, owing to which the secretory activity of these two parts cannot be strictly delimited. The posterior part of the hypophysis begins from the anterior lobe; it surrounds the hypophyseal stalk and then spreads to the base of the brain. Histologically it differs from the structure of the anterior lobe.

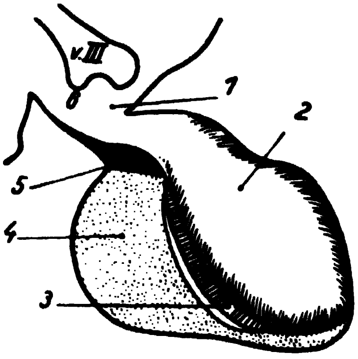


Fig. 175. Lobes of hypophysis.

1—infundibulum; *2*—pars nervosa *3*—pars intermedia; *4*—pars anterior *5*—pars tuberosa; *6*—base of brain; *v III*—edge of 3rd ventricle of the brain

The hypophysis is richly supplied with blood vessels and nerve fibres.

Consequences of Hypophysectomy and Hypophyseal Diseases

Despite the difficulties of surgical access to the hypophysis, the consequences of its removal and injuries to it (application of a glass ring on its stalk by A. Speransky's method) have been studied on animals. Careful surgical removal of the hypophysis does not kill the animal (A. Bogomolets, L. Karlik). Thus, the hypophysis is not an organ indispensable to life.

The most characteristic consequences of hypophysectomy are: 1) stunted growth of young animals (Fig. 177); 2) atrophic modifications of the sex glands, sexual underdevelopment in young animals and loss of sexual function in adult animals; 3) atrophic changes in the thyroid gland and adrenals; 4) profound inanition (cachexia); 5) increased urine production (polyuria).

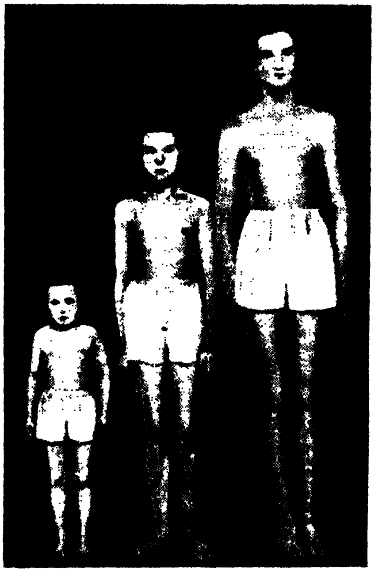


Fig. 176. Boys of same age: left with deficient function, centre with normal function and right—with excessive function of hypophysis.

In man hypophyseal diseases assume various forms. Deficient function of the hypophysis in childhood results in stunted growth, retarded ossification of the cartilages, underdevelopment of the sex organs (*hypophyseal dwarfism*).

The hypophyseal dwarfs, however, remain well proportioned, their intelligence not noticeably affected, which distinguishes them (Fig. 176) from thyroid cretins.

Besides hypofunction of the hypophysis responsible for dwarfism, there are also cases of its hyperfunction. The latter results in gigantism: in these cases individuals grow to two and more metres in height (Fig. 176). Gigantism is caused by retarded ossification of the long bones of the extremities.

As a result of this endocrine dysfunction in an adult in whom ossification has been completed, only the distal parts of the long bones of the extremities (enlargement of hands, feet, fingers and toes) and the bones of the face (the cheekbones and the lower jaw) exhibit renewed growth. This disease, characterized by a pronounced disproportion of different parts of the body and even of the internal organs, is called *acromegaly*.

Other hypophyseal dysfunction is expressed in profound inanition (hypophyseal cachexia) and diabetes insipidus. In the latter case much less water is reabsorbed from the primary urine in the kidneys and enormous amounts of urine containing but little solids are excreted. This entails unquenchable thirst.

Hormones of the Anterior Lobe of the Hypophysis

It has been possible to obtain a number of hormones from the anterior lobe of the hypophysis. Some of them, obtained in a pure form, have been thoroughly investigated as regards their chemical nature and physiological activity.

The growth hormone. The growth hormone has been obtained in a crystalline form. It is a protein body with a molecular weight between 44,000 and 49,000. A daily administration of 0.1 mg. of this hormone to the young hypophysectomized rat (10 injections of 0.01 mg. each) results in a 10-gr. increase in weight. The hormone also affects the growth of the epiphyseal cartilages. Regular administration of the hormone to young animals produces gigantism. Systematic injections of the hormone into grown-up dogs of certain breeds makes it possible experimentally to induce acromegaly in them. Insufficiency of this hormone in man leads to dwarfism, while its excess results in gigantism or acromegaly.

Gonadotropic hormones. The gonadotropic hormones are elaborated in the basophile cells of the anterior lobe of the hypophysis; chemically they are glucoproteids; they also contain glucosamine and mannose. Two of these hormones have been thoroughly investigated. One of them stimulates the growth and maturation of follicles in female animals, while in male animals it stimulates the formation of sperm. The other hormone affects the interstitial elements of the ovaries and is called the luteinizing hormone. It stimulates the formation of the corpus luteum, which in its turn produces progesterone (p. 446); in males it stimulates the development of Leydig's cells in the testes, as well as the secretion of male sex hormones by these cells.

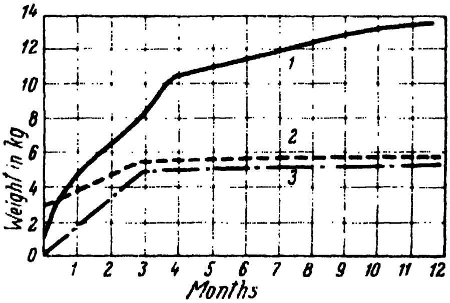


Fig. 1 Increase in body weight during period growth in the normal *(1)* and hypophysectomized pups *(2 and 3)* of same litter (after L. Karlik).

Since these hormones are secreted by the anterior lobe of the hypophysis, its extracts, introduced into the organism of sexually mature animals, can increase the activity of the sex glands (in females, ovulation accompanied by heat; in males, spermatogenesis). In sexually immature animals the administration of hypophyseal extracts stimulates precocious sexuality.

This underlies certain practical measures in the field of pisciculture (N. Gerbilsky). Hypophyseal injections (injections of suspensions of the hypophysis ground in water) to male and female fishes of the Ganoidei order expedite maturation and increase the numbers of mature spermatozoa and spawns capable of fertilization and of further development.

Hormones influencing the activity of other endocrine glands. In addition to the hormones acting upon the sex glands, the anterior lobe of the hypophysis elaborates hormones which stimulate the activity of the thyroid gland (*thyrotropic hormone*) and the adrenal cortex (*adrenocorticotropic hormone*).

The thyrotropic hormone stimulates the growth of the thyroid secretory cells and intensifies their activity. This gives rise to symptoms typical of thyroid hyperfunction. Excessive secretion of the thyrotropic hormone leads to exophthalmos.

Insufficient elaboration of the adrenocorticotropic hormone results in atrophy of the adrenals. Administration of this hormone restores the adrenals.

All the aforesaid hormones are of a protein nature.

The mammotropic hormone. The mammotropic hormone, or *prolactin*, intensifies the secretion of milk by the mammary glands. Lack of this hormone in the blood (for example, as a result of hypophysectomy) stops lactation. Administration of prolactin may evoke lactation even in males. Prolactin is sometimes administered for the purpose of increasing the output of milk in nursing mothers. Like other hormones of the hypophysis, prolactin is of a protein nature. Since strong chemical influences are brought to bear in the process of separation of the six investigated hormones of the hypophyseal anterior lobe, it is possible that the abovementioned hormones are fragments of a lesser number of substances which constitute the source of hormone production. This conclusion is prompted by the fact that only two kinds of cells (acidophilic and basophilic) are, apparently, capable of secretory activity.

Hormones influencing carbohydrate and fat metabolism. Administration of extracts from the anterior lobe of the hypophysis leads to hyperglycemia, glucosuria, increase in acetone bodies in the tissues and their elimination with the urine. This action is called diabetogenic and is accounted for by the existence of a hormone which influences the metabolism of fatty acids. Recent investigations indicate that some of the aforesaid influences on the metabolic processes may be due to the action of the growth hormone. This hormone stimulates storage of protein bodies by decreasing their disintegration and by drawing carbohydrates and fats into metabolism in a compensatory way which in turn leads to accumulation of acetone bodies.

Hormones of the Posterior Lobe of the Hypophysis

Extracts from the posterior lobe of the hypophysis and the medical preparation "pituitrin," obtained from them, also exert a multiform influence on the organism. Firstly, the blood pressure rises due to the constriction of the arterioles and capillaries; secondly, the introduction of pituitrin stimulates contractions of the smooth muscles, particularly the muscles of the uterus; thirdly, the excretion of chlorides by the kidneys increases while diuresis diminishes.

The influence of the posterior lobe of the hypophysis on the blood pressure and on the smooth muscles is connected with the formation of two hormones. The hormone which raises the blood pressure by constricting the blood vessels is known as *vasopressin* (also *pitressin*, and *beta-hypophamine*). This constrictive action affects even the denervated vessels. The hormone which stimulates the contraction of the uterus is called *oxytocin* (also *pitocin* and *alpha-hypophamine*). Both hormones are polypeptides with a molecular weight of about 1,000. Pituitrin and oxytocin are widely used after parturition when it is necessary to induce a sufficiently vigorous contraction of the uterus in order to expel the placenta and stop the uterine haemorrhage.

The hormone which influences the excretion of urine is called the *antidiuretic hormone*. It stimulates reabsorption of water from the primary urine when the latter passes down the renal tubules. Removal of the posterior lobe of the hypophysis leads to the excretion of tremendous quantities of urine by the kidneys, i.e., to polyuria. The same effect is observed when the nervous connections between the brain and the anterior lobe of the hypophysis are impaired.

It should be pointed out that hypophysectomy does not entail polyuria; thus, the exclusion of the function of the posterior lobe manifests itself only in the presence of the hypophyseal anterior lobe.

In diabetes insipidus, a disease characterized by acute polyuria, administration of extracts from the posterior lobe of the hypophysis reduces urine excretion.

Hormone of Pars Intermedia of the Hypophysis

This hormone, called the *melanophorine hormone* (or *intermedine*) affects the pigmental cells of the skin. The action of this hormone has been studied on amphibians and fishes. Under its action the melanophore cells dilate and the pigmental granules in these cells are more evenly distributed. As a result, the skin of the animal darkens.

Modifications in the state of the pigmental cells may be caused by illumination of the retina of the eye. Thus, the secretion of the melanophorine hormone takes place reflexly, in response to the stimulation of the animal's visual apparatus. This mechanism is of essential defensive significance, since pigmentation of the skin changes so much that the colour of the animal approximates that of the surrounding medium and the animal becomes less perceptible to its enemies.

Regulation of Hypophyseal Activity

The hypophysis is connected through its stalk with the hypothalamic region of the brain by nervous pathways. It is innervated by the superior cervical sympathetic ganglion. Impairment of the nervous connections affects the function of the hypophysis.

The influence of the superior cervical sympathetic ganglia on the function of the hypophysis is well illustrated by the facts observed by A. Tonkikh. Dogs and cats whose superior cervical sympathetic ganglia are stimulated (by squashing with pincers) die of pneumonia within three or four days, the pneumonia apparently caused by an excessive supply of certain hormones to the blood. If the hypophysis is removed before the ganglia are squashed pneumonia does not develop. Thus, the endocrine activity of the hypophysis is under constant control of the nervous system. The reflex influence of the retina of the eye on the secretion of the melanophorine hormone has also been convincingly proved. The secretion of gonadotropic hormones in some animals is likewise evoked reflexly from the retina of the eye: they develop heat only in the period when the days grow longer.

K. Bykov and his associates have demonstrated the possibility of elaborating a conditioned reflex which leads to the secretion of the hormone influencing the formation of urine by the kidneys (p. 405).

The blood is not the only medium through which the hypophyseal hormones act on the organism. It is possible that certain hormones act upon the central nervous system by diffusing through the stalk of the hypophysis, or through the spinal fluid.

Sex Glands

(The internal secretion of the sex glands is treated in the next part.)

Epiphysis

The epiphysis (pineal body) is a small body situated above the corpora quadrigemina. The endocrine activity of the epiphysis is believed to inhibit the development of the sex glands. Removal of this gland in sexually immature cocks leads to precocious sexual maturity. No such effect could be discovered in mammals, however; nor was it possible to obtain any hormones from the epiphyseal tissue.

Thymus

The thymus is located in the anterior mediastinal cavity. This gland is believed to function in early childhood, before puberty, its hormone inhibiting the development of the sex glands. The role of this gland is not exactly known as yet. Towards puberty the thymus degenerates.

In some cases the thymus persists into adult life. This is accompanied by an enlargement of the lymphatic glands. This state is designated as *status thymicolymphaticus.*

CHAPTER 44

REGULATION OF ENDOCRINE ACTIVITY

Nervous Regulation of Endocrine Activity

As before stated, the activity of all endocrine glands is under constant control of the nervous system. In some cases an endocrine organ develops by differentiation of nervous tissue. The posterior part of the hypophysis is formed from the floor of the third ventricle. The specialized cells of this part—the pituicytes—are modified neurogliar cells. In addition to chromaffin cells the adrenal medulla contains ganglionic sympathetic cells. The action of adrenalin on various systems of the organism is similar to that of the sympathetic elements of the nervous system. Here the nervous and endocrine influences are so interwoven that one seems to continue the other. The activity of all other endocrine glands, however, is also stimulated or inhibited by the nervous system. Facts to this effect have already been cited. In some cases the secretion is influenced by reflexes caused by the stimulation of certain receptor zones. Reflex stimulation of the secretion of the hypophyseal gonadotropic hormone, which evokes ovulation (maturation of the ovum and of the entire graafian follicle), is an example. In some animals this process takes place after winter when the days are longer. It appears that natural light can be replaced by artificial light. The secretion of this hypophyseal hormone is stimulated reflexly from the retina of the eye. Blind animals prove incapable of reproduction. In rabbits no ovulation takes place until the secretion of the gonadotropic hormone is reflexly stimulated by coitus.

As before stated, it is possible to elaborate a conditioned reflex which leads to the secretion of a hormone influencing urine formation in the kidneys. In this case the nervous influence is consummated humorally. There are reverse relationships as well. It has been demonstrated that secretin, the hormone of the digestive tract, affects the exocrine elements of the pancreas through the nerve endings lining the glandular lobules of the gland.

Relationships between the Endocrine Glands

The organic connections between the nervous and endocrine systems integrate them and ensure the so-called neurohumoral regulation of the functions of the organism.

The relationships within this system are complicated by the fact that the activity of various endocrine glands is interconnected. The stimulating action of certain hypophyseal hormones on the hormone production of the sex glands, adrenals and thyroid has already been described. The thyrotropic hormone is indispensable to the thyroid during the conversion of diiodotyrosine into thyroxin. In some cases one hormone stimulates the action of another hormone, i.e., there is a synergism of hormones. The joint activity of the thyroid hormone and the hypophyseal growth hormone is an example; the former stimulates metamorphosis and bodily development, while the latter stimulates the growth proper. The diabetogenic action of the hormone of the hypophyseal anterior lobe (accumulation of ketone bodies, hyperglycemia) similarly involves the hormones of the adrenal cortex.

Contrariwise, some hormones inhibit the action of other hormones. For example, the hormones of the anterior lobe of the hypophysis and the adrenal cortex reduce the sensitivity of the organism to insulin. Steroid sex hormones curtail the secretion of thyrotropic and gonadotropic hormones by the anterior lobe of the hypophysis. Castration, i.e., removal of the sex glands, results in a development of the basophilic cells which secrete gonadotropic hormones. The sex hormones are, apparently, antagonists of the growth hormone secreted by the hypophysis. The secretion of the growth hormone persists even in adult animals, though the animals cease growing. It is believed that the sex hormones exert antagonistic influences.

Human pathology knows a number of diseases caused by functional disturbances in more than one endocrine gland. For example, diabetes is usually caused not only by the deficiency of the island apparatus of the pancreas, but by disturbances in the function of the hypophysis, and sometimes of the adrenal cortex. In hyperthyroidism exophthalmos usually results from an excessive output of the thyrotropic hormone, etc.

Thus, the functions and metabolism of the organism are not regulated humorally by autonomous action of individual endocrine glands, but by their entire interconnected system under the control of the nervous system. The latter, playing a leading role in the regulation, ensures an adaptive readjustment of the functions and metabolism of the organism in response to the action of agents of the external and internal environment.

PART XI

FUNCTIONS OF THE SEX GLANDS AND REPRODUCTION

CHAPTER 45

FUNCTION OF THE SEX GLANDS

Castration and Transplantation of Sex Glands

The influence of castration on the entire organism has been known since early antiquity, when castration was used for improving draught animals and fattening of cattle. It was definitely established only in the middle of last century, however, that the marked influence of the sex glands on the physique, the growth of hair and the behaviour, was determined by certain substances, elaborated by the testes and ovaries, entering the blood.

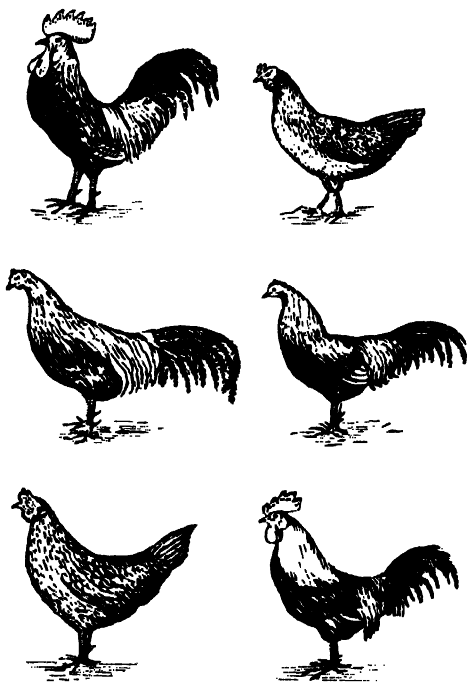


Fig. 178. Left row (top to bottom): normal cock, castrated cock, castrated cock after engrafting of ovaries. Right row (top to bottom): normal hen, castrated hen, castrated hen after engrafting of testes (after M. Zavadovsky).

Transplantation of sex glands to a castrated animal develops in this animal the secondary sexual characters inherent in the sex from which these glands were taken, the former secondary sexual characters often undergoing substantial changes. For example, if the sex glands of the cock are grafted in the castrated hen the latter develops a characteristic cock's comb, and a carriage typical of the cock (Fig. 178). The behaviour of such a masculinized hen resembles that of the cock (aggressiveness, attempts at covering hens, etc.). Contrariwise, transplantation of hen's ovaries to the castrated cock develops the traits of the hen in it. If ovaries are grafted in the castrated mammal the latter develops certain female traits (growth of the mammary glands, changes in the distribution of subcutaneous fat and other feminine characters). It follows that the so-called secondary sexual characters are determined by the supply of one or several hormones from the sex glands to the blood and by their action (through the nervous system) on metabolism and on the formation of the morphological sexual characters.

The secondary sexual characters include all the morphological and functional peculiarities which distinguish one sex from the other (except the peculiarities of the organs directly involved in reproduction and known as the primary sexual characters). The most essential human secondary sexual characters include: 1) peculiarities in the structure of the male and female skeletons (these are treated in detail in courses of anatomy); 2) higher average muscularity of the male; 3) specific distribution of the hair over the body; 4) development of the mammary glands in the female; 5) differences in the timbre of the voice.

The sex organs belong to the primary sexual characters. Their development is also influenced by the sex glands. In the male castrated before sexual maturity the penis, seminal vesicles, Cowper's gland and the prostate are underdeveloped; in the castrated female it is the clitoris, vagina, uterus, and Bartholin's glands which are underdeveloped. Transplantation of sex glands to castrated animals, or injection of corresponding hormones (see below) cause the underdeveloped sex organs to develop normally.

The mechanism which governs the influence of sex hormones on the development of sexual characters is not clear as yet; still less is known about the influence of these hormones on other aspects of the organism's activity. It can only be said that the removal of the sex glands results in certain changes in general metabolism which slightly decreases: the type of metabolism alters and fat accumulates. The available data relating to the influence of castration on the chemism of the blood and on the muscular and nervous systems are contradictory. The statements concerning a decrease in muscular strength as a result of castration are refuted by the age-old experience in utilizing castrated males as draught animals in agriculture. Convincing experiments carried out by M. Petrova show that disturbances in the higher nervous activity may develop in dogs after castration. These disturbances manifest themselves in a weakening of the inhibitory process and in chaotic responses of the animal to the action of signal stimuli.

Development of Male Sex Cells (Spermatozoa) and Formation of Sperm

The formation and development of spermatozoa, the male sex cells, take place in the seminal tubules of the male sex gland (testis, see Fig. 179). An immature sex gland contains cells having large nuclei—spermatogonia, from which at puberty motile cells—spermatozoa—begin to develop. As the spermatozoa develop, motionless cells, so-called cells of Sertoli, are formed; it is supposed that their function is to nourish the spermatozoa.

The specific feature of the spermatozoa is their ability to move independently, which is made possible by the contractile elements in their tails and is stimulated by various substances in the surrounding medium. An important role in this respect is played by the carbohydrates in the fluid surrounding the spermatozoa (for example, fructose in the secretion of the prostate gland). Spermatozoa can also move in a medium containing no oxygen because of the energy derived from glycolytic reactions. The secretion of the prostate is, apparently, of the greatest importance in stimulating the movements of the spermatozoa. On entering the *vas deferens* the spermatozoa move forward and are stored in the seminal tubules up to the moment of copulation. Contractions of the seminal vesicles propel the fluid secreted by these vesicles into the urinogenital canal—the urethra. Here the secretions of the seminal vesicles and of the prostate gland are joined by the secretion of Cowper's gland located in the cavernous part of the urethra. Thus, the sperm ejaculated during copulation represents a secretion of all the aforesaid glands in which an enormous number of spermatozoa are suspended. In man the number of spermatozoa ejaculated during one sexual act exceeds 200 million, of which only one usually fertilizes the ovum.

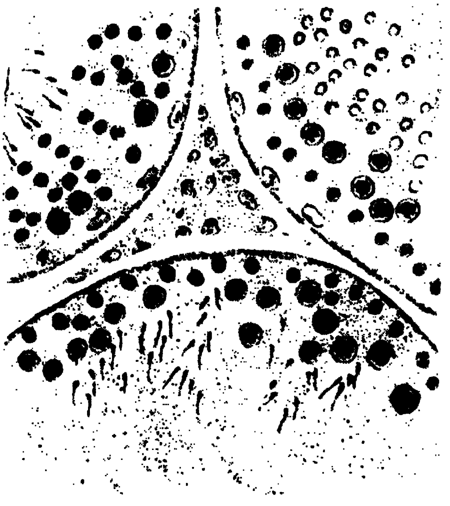


Fig. 179. Diagrammatic section of portion of the rat's seminiferous tubule.

It has now been found that the ovum can be simultaneously fertilized by many spermatozoa. Substantial modifications of the hereditary properties of the embryo are therefore possible. Many spermatozoa become implanted in the tissue of the female sex organs (details will be found below).

The male sex glands develop in the abdominal cavity of the embryo and descend into the scrotum only at a later foetal period. This process is closely connected with the changed environmental conditions which are important to the function of the testes. Usually there is no spermatogenesis when the testes fail to descend into the scrotum (so-called cryptorchidism).

In cryptorchidism the testes located in the abdominal cavity are subjected to a constant influence of high temperature which retards the development of the seminal tubules. Experimental investigations of animals show that an increase in the temperature of the testes suppresses spermatogenesis. The same phenomenon is observed in fevers.

Spermatogenesis is regulated through the hypophyseal hormones (see below). Removal of the hypophysis leads to a sharp decrease in spermatogenesis. Administration of hypophyseal gonadotropic hormones to hypophysectomized animals intensifies spermatogenesis.

The nervous influences on spermatogenesis are not clear as yet, though certain modifications of spermatogenesis undoubtedly produced reflexly (probably through reflex influences on other endocrine glands) are known. These include the modifications of spermatogenesis under changed conditions of lighting and temperature in the external environment.

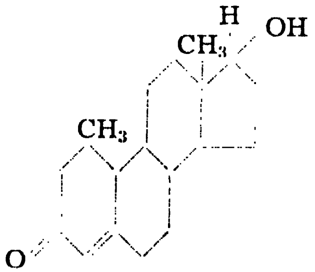
Internal Secretion of the Male Sex Glands

Testosterone, the male sex hormone, is a specific stimulator of the development of the sex organs and of secondary sexual characters in the male organism. In a growing male the presence of testosterone in the blood at puberty is a sine qua non for the emergence of the sexual instinct and the induction of erection without which the sexual act is impossible.

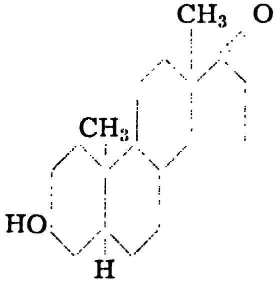
Similar effects may be produced by certain metabolites of testosterone and related chemical compounds. This is why all substances (including testosterone) capable of stimulating the development of secondary male sexual characters are covered by a common name—*androgens.*

Unit of male sexual hormone. The concentration of testosterone, or other androgens, may be disclosed and quantitatively estimated by using the action of these substances (and, consequently, of the products which contain them, i.e., the blood, urine, testicular extracts, etc.) on various biological objects; castrated cocks and castrated male mice are most suitable for this purpose. The most characteristic index of the administration of androgens to cocks is the growth of the comb. The unit of the male sex hormone (the "cock's unit") is the minimum dose required to make the comb grow by 15 per cent after four days' injections. The growth of the seminal vesicles resulting from the administration of testosterones or other androgens serves as the criterion for estimating the activity of the hormone in castrated male mice.

Structure and transformations of the male sex hormone. In their structure the male sex hormones are close to those of the female. Androsterone, a less active substance excreted with the urine, is also related to testosterone. The testosterone, elaborated in the testes, is continuously converted in the organism into androsterone. Injection of large doses of testosterone into man or chimpanzee increases excretion of androsterone with the urine. The liver plays an important role in inactivating testosterone; vitamin B deficiency reduces the ability of the liver to inactivate the androgens.



Testosterone



Androsterone

Site of male sex hormone formation. Testosterone, the male sex hormone, and androsterone, its metabolite isolated from the urine, are elaborated in the testes, the bulk of the hormones being secreted by the so-called Leydig's interstitial cells. This is indicated by a number of facts. For example, in cryptorchidism the seminal tubules are underdeveloped, while the interstitial cells are developed normally. The accessory glands and the secondary sexual characters are also normally developed. It follows that adequate quantities of androgens are elaborated in this state.

Histochemical investigations using the phenylhydrazine test also show that testosterone is formed in the interstitial cells. Very active androgens are also formed in the adrenal cortex.

Significance of the male sex hormone. All male sexual characters develop under the influence of the male sex hormone (distribution of hair, masculine type of the skeleton and fat accumulation, pitch of the voice, development of the penis, the prostate and the seminal vesicles).

It should be emphasized that action of the male sex hormone on the organism is connected with the activity of the central nervous system, particularly the cerebral cortex, its higher division. Secretion of the sex hormone puts the central nervous system in a state which under the action of definite, so-called ecologo-sexual factors of the external environment (see page 449) manifests itself in sexual excitement. Various agents coinciding in time with this excitement become conditioned stimuli which evoke conditioned reflexes connected with the sexual function and sexual behaviour. These conditioned reflexes play an important role in the formation of the reproductive functions of the male organism. Their role is also revealed in the fact that the ability for coition may persist for a long time even after castration, if the latter was performed after puberty.

Physiology of the Ovaries

Cyclically recurring morphological and functional modifications are observed in the ovaries from puberty to the extinction of the sexual function (climacteric). These modifications are connected with considerable changes in other tissues and organs, and in the entire behaviour of the organism, and are known as *sexual cycles*.

The course of these sexual cycles is determined by the periodic maturation of ovarian follicles which in all mammals (except man and simians) is called the *oestrous cycle* (oestrus meaning "heat"). In primates and man the sexual cycles are called menstrual, since *menstruation* is the most pronounced external characteristic of this cycle. The menstrual cycles also reflect the functional modifications in the ovaries, but differ from the oestrous cycles by more complex alterations in the uterus and other organs.

The ovary of an adult woman consists of the germinal epithelium which invests it and of the cortical and medullary substance. The cortical layer of the ovary contains a large number of follicles at different stages of development (Fig. 180). The bulk of the follicles are at the stage of the so-called primordial follicle consisting of an *ovocyte,* egg cell, surrounded by epithelial follicular cells. The transformation of these primordial follicles into mature, or *graafian follicles*, is accompanied by a growth of the ovocyte. The follicular cells surrounding such a maturing ovocyte proliferate forming a follicular membrane or *granulosa.* The connective tissue surrounding the primordial follicle forms a connective-tissue membrane or *theca folliculi* divided into the external and internal membranes and richly supplied with blood vessels. The maturing follicle fills with fluid and projects from the surface of the ovary (into the abdominal cavity).

In the mature graafian follicle (Fig. 180), which is a macroscopically visible structure (about 2 mm. in diameter), the ovum is located on a special epithelial prominence and is surrounded by a heap of granulosa cells *(corona radiata)* together with which the ovum is discharged into the abdominal cavity after the rupture of the follicle.

The phase of follicular maturation terminates by the rupture of the follicle which is accompanied by the discharge of the ovum into the abdominal cavity. This process is called *ovulation.* The immediate causes which stimulate the rupture of the follicle are: action of proteolytic enzymes contained in the liquor folliculi on the follicular membrane; dilation and increased permeability of the blood vessels in this connective-tissue membrane of the follicle; perspiration of the fluid and increased pressure in the liquor folliculi. Upon its discharge into the abdominal cavity, the released ovum is directed first to the fimbriated end of the fallopian tube and then into the tube itself.

After the discharge of the ovum the remaining portions of the graafian follicle change into the *corpus luteum*, a temporary functioning gland of internal secretion.

The following four stages are distinguished in the development of the corpus luteum: 1) growth, 2) glandular transformation, 3) maximum development, and 4) degeneration.

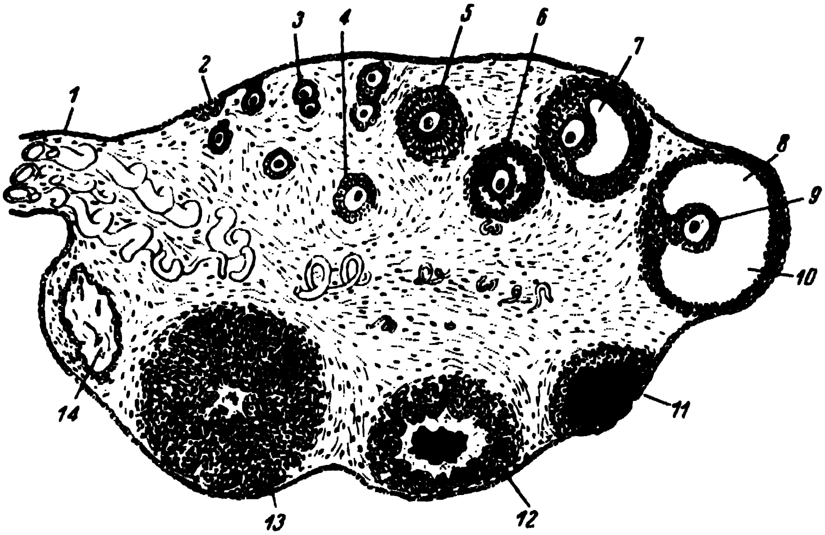


Fig. 180. Diagrammatic section of the guinea-pig's ovary.

1—blood vessels; *2, 3, 4, 5, 6*—primary follicles at different stages of development; *7*—graafian follicle; *8*—mature graafian follicle; *9*—ovum surrounded by granulosa; *10*—cavity of mature graafian follicle; *11* and *12*—corpora lutea at various stages of development; *13* and *14*—atretic follicles.

The first stage is characterized by a haemorrhage into the cavity of the ruptured graafian follicle and by simultaneous hypertrophy of the epithelial membrane. The second stage is marked by a vascularization of the clot of blood formed as a result of the rupture of the follicle during ovulation and by a transformation (metaplasia) of the epithelial cells containing yellow granules—a substance called *lutein* (hence the term "corpus luteum"). Such is the appearance of the corpus luteum in the third stage of its development, i.e., its maximum development, when it discharges its main hormonal function (Fig. 180). The fourth stage is characterized by a fatty degeneration of the luteal cells and a degeneration of the connective-tissue membranes. The corpus albicans, a connective-tissue scar formed in place of the corpus luteum, gradually resolves in the course of about five years.

If the ovum discharged into the abdominal cavity passes into the fallopian tubes and is not fertilized, the corpus luteum, as an endocrine gland, does not persist for more than 14 to 18 days during which time it goes through all the aforesaid stages of development. If the ovum has been impregnated, the corpus luteum becomes the *corpus luteum of pregnancy*, a structure considerably larger in size and functioning for several months.

Some follicles do not mature and degenerate at different stages. This process known as *atresia* takes place before puberty, all through sexual maturity and during pregnancy.

In old age the foregoing processes, i.e., formation of graafian follicles and ovulation, gradually cease.

Menstruation. It is assumed that normally ovulation (the rupture of the follicle, the passage of the ovum into the abdominal cavity and from there into the fallopian tube) takes place 13 to 15 days (an average of 14 days) before each period of menstruation. With the most frequent cycle (28 days) this corresponds to the midpoint of the intermenstrual period. The follicle matures in the first half of the intermenstruum; the corpus luteum forms and grows in the second half and (in absence of pregnancy) degenerates towards or during menstruation (Fig. 181).

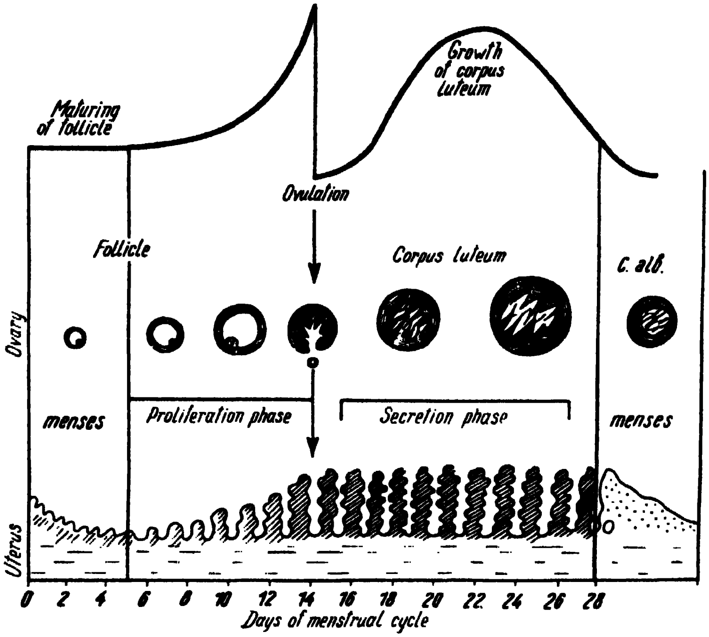


Fig. 181. Diagram of changes in uterus and ovaries during menstrual cycle (after Unggers, with changes).

C. alb - corpus albicans.

This cycle developing in the ovary is accompanied by characteristic modifications of the mucous membrane of the uterus (endometrium). After menstruation the uterine mucosa becomes thin and little vascularized. During follicular maturation it grows progressively thicker and its glands longer, though the latter do not secrete. This is the so-called proliferation phase. After ovulation the glands of the uterine mucosa grow larger and begin to secrete, while their ducts become convoluted. This is the so-called secretion phase (approximately 10 to 12 days before menstruation).

Menstruation, i.e., the flow of blood from the uterine mucosa, only terminates a series of changes which are determined primarily by the cyclical modifications in the ovary. From 50 to 200 ml. of blood are discharged during menstruation, the blood being almost noncoagulable, with high concentration of oestrogenic hormones (see below) and containing mucus. Menstruation is not always connected with the preceding ovulation. There are cases of menstruation without ovulation, for example, the first few menstruations in girls and the menstruation at the beginning of lactation after childbirth.

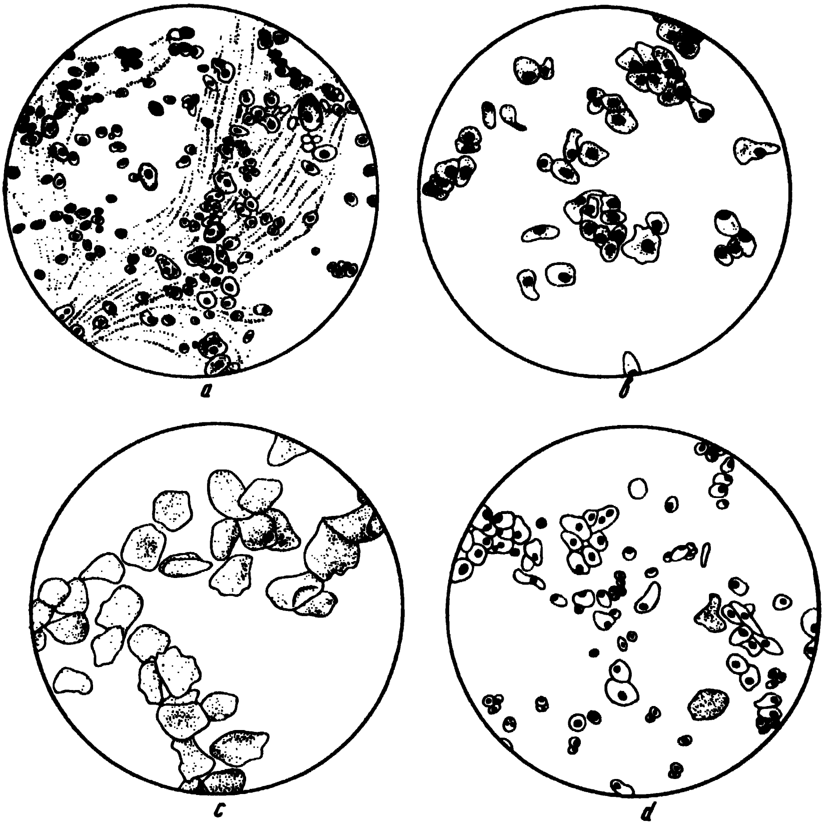


Fig. 182. Microscopy of vaginal smears during oestral cycle in mice.
a — oestral stage; *b*—post-oestral stage; *c* —inter-oestral stage; *d*—pre-oestral stag

The entrance of ovarian hormones into the blood (see below) is indispensable for the onset of menstruation.

The period of menstruation is usually accompanied by changes in the entire organism: enlargement of the thyroid, apparently increased supply of thyroxin to the blood, modifications of the state of the nervous system, certain (slight) alterations in metabolism, pulse rate and stroke volume of the heart.

The oestrus cycle and heat. The sexual cycles in all animals, except primates, are called oestrus cycles. In rats and mice all changes taking place during these cycles serve as criteria for the detection of active substances—hormones—in the internal organs, blood and urine. In rodents (rats and mice) the sexual cycle consists of the following stages (Fig. 182):

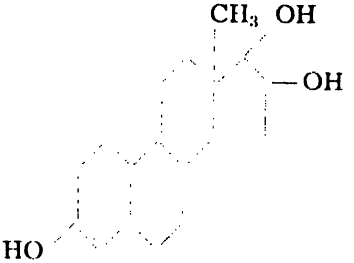
1. Dioestrus (sexual quiescence); lasts from 54 to 60 hours	1. The follicles and the uterus are small-sized, the latter is poor in blood. The vaginal epithelium is thin
2. Praeoestrus; lasts 12 hours	2. The ovary contains mature follicles. The uterus swells. The vaginal epithelium grows thicker
3. Oestrus; lasts from 24 to 30 hours	3. The graafian follicles are ruptured; the uterine mucosa is thickened to the maximum. A layer of cornified cells appears in the vagina. The female allows the male to approach it
4. Metaoestrus; lasts six hours.	4. Corpora lutea are observed in the ovary; the uterus and the vaginal epithelium grow thinner.

In rats and mice this entire cycle repeats rhythmically every four to five days and is shown in the characteristic changes in the vaginal smears (Fig. 182). The oestrous cycle in rodents is distinguished by the fact that the corpora lutea, which are formed during this cycle, do not function without preliminary mating. In rodents mating, even without subsequent impregnation (for example, with a male whose seminal ducts have been ligated), causes the corpora lutea to function and results in so-called pseudopregnancy. The latter is due to a reflex mechanism. A mechanical or electrical stimulation of the cervix of the uterus in mice and rats produces pseudopregnancy.

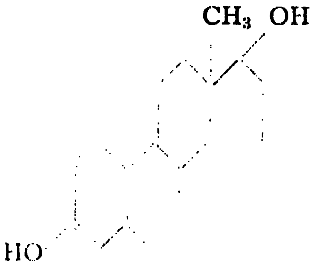
In many mammals (cows, dogs, etc.) the sexual cycle consists of the proliferation phase, during which the follicle matures, and the secretion phase which corresponds to the period of development of the corpus luteum. As a rule, ovulation in mammals coincides with the period of heat. In man and simians ovulation occurs approximately in the middle of the intermenstrual period. Hence the difference between heat and menstruation: the former corresponds to ovulation, i.e., appears at the height of the process which develops in the ovary, while the latter actually terminates the entire cycle, emerging, as before stated, after the function of the corpus luteum has been extinguished and does not coincide in time with ovulation.

Ovarian Hormones

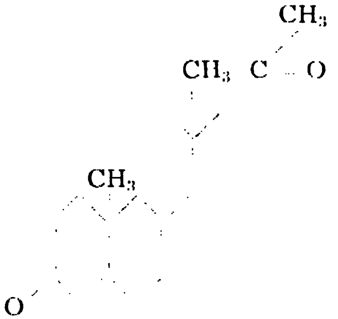
The development of the sex organs and of the secondary sexual characters in a female organism is possible only when the hormone, elaborated in the ovaries, enters the blood. The peculiar effect of this hormone has first been established on castrated females in which an injection of liquids containing this hormone produces the oestrus. The least amount of the female sex hormone which is sufficient to cause oestrus in a spayed mouse has been termed a mouse unit (MU). By its nature the female sex hormone is a compound which is close to cholesterine, i.e., belongs to the class of sterones which includes all other sex hormones. Owing to its ability to induce oestrus this hormone is called *oestrogenic*. It has now been established that the follicles of the ovary elaborate *oestradiol* which is the most active of all natural oestrogens. In other tissues oestradiol is converted into *oestrone* and into less active *oestriol*. In subcutaneous injection oestradiol is almost 100 times as active as oestriol. Besides the ovary, oestradiol is elaborated in the placenta; large quantities of it are contained in the urine of pregnant women. The content of free oestrogens in the urine increases before ovulation, menstruation and delivery.



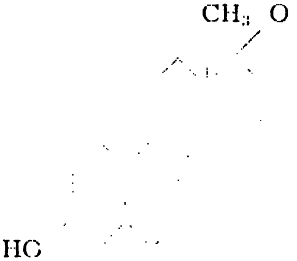
Oestriol



Oestradiol



Progesterone



Oestrone

The concentration of oestrogens is particularly high in the liquor folliculi before ovulation and in the menstrual excretions. Preparations of the female sex hormone are often called folliculin.

Action of oestrogens. Normally the injection of oestrogens produces no distinct changes in the woman's organism, but after removal of the ovaries (inevitable, for example, in cases of tumours) the injection of this hormone in combination with the hormone of the corpus luteum (see below) sometimes makes it possible to some extent to recover the lost sexual cycle and to safeguard the operated woman against the symptoms of castration (it will be observed, however, that castration of a mature woman does not always rapidly modify the traits characterizing the female organism). Manifestations of infantilism (sexual underdevelopment) can, apparently, also be eliminated with the help of this hormone. Oestrogens find also extensive application in gynaecological practice.

Repeated injections of large doses of oestrogens into the organism of males may feminize them. In castrated males this feminization (growth of the mammary glands and changed behaviour towards animals of the opposite sex) manifests itself even after injections of relatively small doses of this hormone.

Hormone of the corpus luteum. The characteristic changes, which take place in the uterine mucosa during the secretory period of the sexual cycle, the discontinuance of ovulation and the development of the mammary glands during pregnancy, i.e., the changes which occur during the growth of the corpus luteum, have given rise to the supposition that the latter possesses a secretory function. This supposition was substantiated by the fact that in rabbits in whom ovulation results only from sexual intercourse the latter causes pseudopregnancy even in the absence of impregnation. The corpus luteum develops, the mammary glands become enlarged and the uterine mucosa modified. The hormone of the corpus luteum was isolated in a pure form and called *progesterone* (evoking pregravidity) or *progestin*. Chemically this substance also belongs to sterones and is close to oestrogens.

From the fourth month of pregnancy the hormone of the corpus luteum is elaborated in women in the placenta, while the corpus luteum of the ovary undergoes involution. By virtue of this pregnancy in women will proceed normally from the fourth month even if both ovaries are removed, which is inevitable, for example, if they develop tumours. In rabbits the corpus luteum and its endocrine function are retained almost to the end of pregnancy, the placenta producing no progesterone. This is why the removal of the corpora lutea (or ovaries) always terminates pregnancy in them.

The action of progesterone is highly diverse—it ensures the growth of the fertilized ovum and stimulates the development of pregnancy. Here are some aspects of its action upon the female organism.

By exerting an influence on the uterus, progesterone determines the secretory activity of its glands (secretion phase). This modification of the uterine mucosa, its "loosening" by the ramifying glandular ducts, is necessary to enable the fertilized ovum, after its passage from the fallopian tubes into the uterus, to attach itself to the uterine wall. Thus the action of progesterone prepares the uterine mucosa for the attachment of the fertilized ovum and makes it possible to convert the uterine mucosa into a decidual membrane.

Progesterone influences the gonadotropic secretion of the hypophysis (page 430), and the state of the nervous system through the nervous centres of the hypothalamic region; it reduces the excitability of the muscular elements of the uterus and ensures the immobility of its walls; together with other hormones it stimulates the hypertrophy of the mammary glands (page 431). The hormone of the corpus luteum inhibits ovulation, stimulates the passage of the ovum through the fallopian tube and helps to preserve the viability of the ovum and its nutrition until it is firmly attached to the wall of the uterus.

Progesterone is determined biologically by its capacity to modify the uterine mucosa in a young sexually mature rabbit. One mg. of the chemically pure preparation contains enough hormone to elicit secretory changes in the rabbit's endometrium for a period of five days. The hormone is also effective when applied directly to the uterine mucosa.

Mechanisms Regulating the Activity of the Sex Glands

The physiological mechanisms which determine the activity of the sex glands in the male and female organisms largely depend on complex nervous influences exerted through the higher divisions of the central nervous system on the hormonal function of the hypophysis.

It has now been established that there are numerous nervous connections between the nuclei of the diencephalon, which are influenced by the cerebral cortex *(nucleus supraopticus* and *nuclei tuberis cinerei),* and the hypophysis. In addition, the hypophysis is innervated by the cervical sympathetic trunk. Many facts show that nervous impulses may act through various efferent pathways of the vegetative nervous system upon the gonadotropic function of the hypophysis, and thereby on the sexual function. For example, adrenalin inhibits the function of the male and female sex glands. There are indisputable facts proving the extreme importance of the nervous system in the regulatory influence of the hypophysis on the sex glands. If, for example, the hypophyseal stalk in a female rat is transected, i.e., if the influence of the nervous system on the function of the hypophysis is excluded, this animal does not exhibit any changes in the sexual (oestrous) cycles which normally occur when there is a drop of temperature in the external environment.

The secretion of the luteinizing hormone, produced in rabbits by copulation, is stimulated through the hypothalamic region and likewise disappears after the transection of the hypophyseal stalk.

Though stimulation of the cervix uteri in rats with the cerebral cortex removed provokes pseudopregnancy (secretory activity of the corpus luteum), and copulation results in normal pregnancy and normal delivery, the maternal instinct in these rats is completely absent.

In females of a number of mammals (for example, in rabbits) unmated for a long time the mature ovary follicles are inactive and only the sexual act leads to the rupture of the follicles which occurs 10 to 12 hours after copulation in rabbits and 40 to 50 hours in cats and polecats.

In rabbits normal ovulation is observed after anaesthesia of the vagina and subsequent copulation. The phenomena which arise in this case apparently depend not only on reflex influences from the receptors of the vagina, but also on those of a number of other receptors. It has been found that ovulations may occur in women in excess of the normal cycle; they may be caused by various influences, including nervous excitation connected with the sexual act.

It should be pointed out that despite the very rich innervation of the ovary, established morphologically, very little was known about the significance of this innervation until recently. Since the ovary of the rabbit grafted in the anterior chamber of the eye undergoes the same changes under the influence of the hypophyseal hormones as an ovary with its innervation intact, the significance of this innervation was denied altogether.

However, recent investigations conducted in the laboratories headed by K. Bykov and in other physiological laboratories have found that the stimulations proceeding from the receptors of the sex organs exert a marked influence on a number of physiological functions. It turns out that the female sex apparatus possesses well-developed interoceptive connections. Thus, mechano- and baroreceptors have been found in the wall and ligaments of the uterus; stimulation of these receptors brings about changes in remote organs, for example, changes in the sensitivity of the rod apparatus of the eye. The uterine blood vessels have been found to have chemoreceptors whose stimulation causes reflex changes in respiration and blood pressure. In pregnancy the sensitivity of these receptors to chemical stimuli increases. Chemoreceptors and thermoreceptors have also been found in the ovaries, uterus and vagina. It is generally characteristic that the sensitivity of all kinds of receptors in the uterus greatly varies with the concentration of sex hormones. Mechanoreceptors whose stimulation modifies respiration and blood pressure have been discovered in the testes.

It has been established by numerous researches that the removal of the hypophysis eliminates the stimulating action of lighting on the sexual function (see below). Similarly, copulation is not followed by ovulation in hypophysectomized rabbits. In hypophysectomized rats it is impossible to cause pseudopregnancy by stimulating the cervix uteri. Thus, the external environment influences the function of the sex glands neurohumorally through the central nervous system; the latter transmits the impulses, which reflexly arise in it, to the hypophysis whose gonadotropic hormones in their turn act upon the internal secretion of the sex glands.

Dependence of the Sex Glands on the Hypophysis

As before stated, the hypophysis elaborates several hormones which stimulate the endocrine activity of many hormone-producing glands, the sex glands in particular. The influence of the hypophysis on the latter is of a particularly pronounced character.

Removal of the hypophysis, like that of the sex glands, always entails symptoms of castration. Administration of an extract from the anterior lobe of the hypophysis to sexually immature animals induces premature development of the secondary sexual characters and the sex organs. In castrated animals, however, the hypophyseal extract does not eliminate the consequences of castration. It follows that the anterior lobe of the hypophysis elaborates hormones which influence the sex glands and thus determine the activity of the latter. These hypophyseal hormones are called *gonadotropic hormones.*

The gonadotropic hormones do not possess any specific sex features. This means that the same hormones are elaborated in the hypophysis of the female and of the male. The specific character of their action is determined, so to speak, by the properties of the "addressee": in the male organism they act upon the testes, while in the female organism upon the ovaries.

The anterior lobe of the hypophysis elaborates two hormones whose action is of a gonadotropic nature: 1) a follicle-stimulating hormone, and 2) a luteinizing hormone; prolactin also acts gonadotropically (page 432). These hormones have been isolated in the form of purified protein substances and their biological action has been studied on hypophysectomized animals.

The follicle-stimulating hormone induces the growth of follicles in females, and, subsequently, their atresia without the formation of corpora lutea. In males it somewhat stimulates the development of the seminal tubules.

In females the luteinizing hormone recovers the interstitial tissue of the ovaries which is atrophied after hypophysectomy; it also stimulates the transformation of the follicles into corpora lutea. In males it stimulates the development of Leydig's cells and the elaboration of androgens. The latter, together with the follicle-stimulating hormone, stimulates spermatogenesis.

Prolactin contributes to the elaboration of progesterone by the corpora lutea in females (its significance for lactation is described below); the role played by this hormone in males is so far unknown. In females the joint action of the follicle-stimulating and luteinizing hormones of the hypophysis induces maturation of follicles, ovulation, development of the corpora lutea and secretion of oestrogens.

Chorionic gonadotropin, a special hormone, somewhat similar in biological action to that of the gonadotropic hormones of the hypophysis is elaborated in the villous membrane of the foetus (chorion) and later in the placenta during pregnancy. However, chorionic gonadotropin does not affect hypophysectomized animals. Chorionic gonadotropin prolongs the stage of maximum development of the corpus luteum and intensifies its secretion of progesterone. The blood and urine of pregnant women contain large amounts of chorionic gonadotropin.

Excretion of gonadotropic hormones into the urine and early diagnosis of pregnancy. It is known that excretion of gonadotropic hormones into the urine greatly increases during pregnancy.

The amount of gonadotropic hormone, which stimulates the sex glands, sharply increases in the urine of pregnant women and some simians from the very beginning of pregnancy. Early diagnosis of pregnancy, which is of great practical importance (for example, when extra-uterine pregnancy is suspected), is based on this phenomenon. The diagnosis consists in the following: 1.5 to 2 ml. of a woman's urine is injected into a three- or four-week-old (immature) female mouse six times in the course of two days. If symptoms of maturation are clearly revealed in the ovary of the mouse (haemorrhage into the graafian follicles, showing as red points under a magnifying glass, and formation of the corpus luteum) within four days, the given urine contains chorionic gonadotropin and belongs to a pregnant woman. It is even more convenient to use a mature or immature female rabbit; 24 to 48 hours after a single injection of the urine of a pregnant woman into the aural vein of the rabbit (that is, after the introduction of the gonadotropic hormone into the blood) haemorrhagic follicles and luteinization are observed. Ejection of spermatozoa into the cloaca of male frogs and toads, and spawning of female loaches after the introduction of the urine of pregnant women into these poikilothermal animals may also serve for diagnosing pregnancy.

Importance of secretion of the gonadotropic hormone. The secretion of humoral stimulators of the sex glands by the anterior hypophyseal lobe is a very important mechanism by which the central nervous system regulates the activity of these glands. It is assumed that sexual maturation is determined by the entrance of the hypophyseal gonadotropic hormones into the blood. Certain cases of early sexual precocity (a case of pregnancy of a six-year-old girl has been described) are probably due to a premature supply of this hormone to the blood. The extinction of sexual activity due to certain lesions of the hypophysis (acromegaly, etc.) is caused by arrested supply of the gonadotropic hormone to the blood. The environmental agents act on the sex glands mainly through reflex influences on the function of the hypophysis.

Influence of the sex glands on the function of the hypophysis. In castrated animals the amount of the follicle-stimulating hormone increases. It may therefore be assumed that in this respect the influence exerted by the internal secretion of the ovary on the hypophysis is opposite to that which is exerted by the hypophysis on the ovary. Contrariwise, the formation and secretion of the luteinizing hormone is stimulated by the ovarian hormones; while suppressing the secretion of the follicle-stimulating hormone, the oestrogens always stimulate the secretion of the luteinizing hormone. Progesterone, administered in small doses, stimulates the secretion of the luteinizing hormone and inhibits it when administered in large doses.

Influence of the External Environment on the Sexual Function

The importance of external influences on the function of the sex glands (both ovaries and testes) has long been known, but the mechanism of these influences is not quite clear as yet.

The influence of the external environment tells with particular force on the sex glands and the sexual activity of animals whose reproduction is confined to a definite season. The most important factor which influences the ovaries is the action of the rays comprising the visible part of the spectrum. Svetozarov and Shtraikh have shown that prolonged "daytime" induces development of the ovaries in birds normally observed only in spring. Some birds begin to nest only in the presence of a definite microlandscape, for example, bushes, hollows in trees, certain kinds of soil, etc. The sex stimulus is also of great importance to the activity of the sex glands. Some researchers (A. Mashkovtsev et al.) have found that the very presence of a male in a herd of animals can stimulate the development of the ovaries even without any direct sexual excitement. These facts, established for a number of agricultural animals and birds, are of great practical significance.

The influence of stimuli acting upon the sexual functions with the participation of the cerebral cortex has been proved by numerous observations. It includes the aforesaid action of the so-called oecologo-sexual stimuli, when various factors of the external environment modify the course of the sexual activity. Many cases are known when the menstrual cycle in women becomes deranged under the influence of emotional stress.

CHAPTER 46

PHYSIOLOGICAL PROCESSES OF REPRODUCTION

The function of reproduction is a complex of physiological processes ensuring preservation of the species. Vertebrates reproduce themselves only sexually. All reproductive processes may be divided into processes of formation of the sexual products—ova and spermatozoa, processes of copulation and fertilization, and processes connected with the development of the foetus (pregnancy). These extremely complex phenomena are linked up with a number of complex physiological changes in the organism, changes in its reflex activity and metabolism, and some morphological changes. Since the reproductive processes are closely related to the general nature of the animal's vital activity and, above all, to the conditions of its existence in the external environment, many of them are strictly dependent on the rhythm of a complex of environmental factors, particularly lighting conditions, temperature, peculiarities of landscape, etc. This determines the numerous rhythmic variations in the reproductive function based on seasonal and other rhythms.

The rhythmic changes in the reproductive function, which greatly differ in animals, are connected with their natural surroundings; these phenomena, considerably modified, also occur in man. The rhythmic course of the reproductive processes is most clearly expressed in morphological and functional changes in the ovaries connected with the development and maturation of the ovum, ovulation and changes in the secretion of hormones which exert a tremendous influence on the organism.

The cyclic character of sexual activity is usually less pronounced in males, though it is also quite distinct in the males of many wild mammals (beasts of prey and certain rodents).

Profound morphological modifications of the sex glands are accompanied by marked changes in the physiological state of the animals and in their behaviour. First of all they include phenomena of sexual excitement (libido) which is accompanied and determined by a number of reflexes of a nature of unconditioned inborn activity. The entire complex of sexual reflexes ensures the act of fertilization, i.e., the union of the ovum and the spermatozoon.

The process of fertilization in mammals, birds and reptiles takes place in the sex organs of the female, while in most fishes and amphibians it occurs in the water into which both the female and male sexual products are ejected.

Physiology of Conception

Conception consists in direct contact of one or several of the spermatozoa delivered into the female organism with the ovum discharged into the female genital tract as a result of the rupture of a ripe graafian follicle.

The spermatozoa are introduced into the female genital tract in the sexual act (copulation) during which the male copulative organ (penis) is inserted into the vagina.

In all mammals the introduction of the penis into the vagina is preceded by a state of sexual excitement expressed in the erection of the penis. Erection is accompanied by an active dilation of the vessels of the penis, the flow of blood increasing here eight- to tenfold. In addition, the *m. ischio-cavernosus* contracts and compresses *v. dorsalis penis*. Thus, not only the supply of blood, but also the filling of the male sex organ with blood increases. In man and in a number of mammals erection is accompanied by a relaxation of *m. retractoris penis*. During copulation the female sex organs react by changes in the filling of the clitoris and vulva with blood. These changes are accompanied by considerable secretion from Bartholin's glands situated at the entrance to the vagina. The stimulation of the receptors of the glans penis during its friction against the wall of the vagina causes reflex contractions of the vasa deferentia and seminal vesicles. The sperm, a complex fluid consisting of secretions of the epididymis, seminal vesicles, prostate gland, and Cowper's gland and containing spermatozoa, is propelled through the urethra by contractions of *mm. bulbo-* and *ischio-cavernosi* and ejaculated.

The uterus moves at the same time and its axis assumes a position corresponding to that of the vagina.

Due to their active motility, the spermatozoa, which are contained in the sperm in great numbers, pass from the vagina into the uterine cavity and then travel up the fallopian tubes where the union of the spermatozoon and the ovum, i.e., fertilization, usually takes place.

The fertilized egg is then carried to the uterus by contractions of the fallopian tubes and becomes implanted in the uterine mucosa.

The nervous mechanism of the sexual act is a series of relatively simple spinal reflexes which normally, however, always form part of a complex reflex act involving the higher divisions of the brain. Artificially the sexual act can be performed even after transection of the spinal cord in the thoracic division. The cell bodies of the spinal neurons whose fibres innervate the sex organs form spinal centres of erection and ejaculation situated in the lumbar division of the cord. The external genitalia are peripherally innervated by sympathetic and parasympathetic fibres. The latter issue from the sacral division of the spinal cord.

Stimulation of the sympathetic fibres (passing through the sacral ganglia) causes constriction of the penile arteries and contraction of the smooth muscles of the scrotum and of *m. retractoris penis*. The sacral nerves contain both parasympathetic and motor fibres. Stimulation of the parasympathetic fibres leads to active dilatation of the vessels of the external male and female genitalia, inhibition of the smooth muscles of the penis and relaxation of *m. retractoris penis*.

The motor fibres of the sacral nerves innervate *mm. ischio-* and *bulbo-cavernosi* and the muscles of the urethra; in the female they innervate the muscles of the clitoris and of the sphincter vaginae.

The internal female sex organs are innervated by sympathetic nerve fibres which pass through the inferior mesenteric ganglion. Stimulation of these nerve fibres causes contraction of the uterus and vagina. In the male, stimulation of the sympathetic fibres results in contraction of the smooth muscles of the vasa deferentia and seminal vesicles.

Normally, cortical signalization is enormously important to the libido and the performance of the sexual act.

By using requisite methods of disinhibition it is possible considerably to intensify the sexual activity of sires which is of prime importance to pedigree cattle-breeding.

Pregnancy and the Physiology of the Foetus

As soon as the ovum is fertilized, usually in the fallopian tube, it begins to cleave. Some time later (in about eight days) the fertilized ovum descends into the uterus by which time it is already at the blastular stage.

Fertilization is preceded by secretory (pregravidic) modifications of the uterine mucosa, which consist in a rapid growth of the mucosa with certain changes in the stroma and the glandular apparatus. The uterine mucosa grows almost four times as thick and its glands become corkscrew-shaped. Until then the glands of the uterine mucosa, though enlarged, produce no secretion. These glands begin to secrete after the fourteenth or fifteenth day of the menstrual cycle. The glands grow still larger and their lumen considerably expands. If the ovum is fertilized the modified uterine mucosa, instead of disintegrating to one-fifth of its thickness and being carried away with the blood and mucus, continues to grow thicker. In this case the uterine mucosa is divided into two layers: a compact layer and a deeper, spongy layer. The latter consists of a connective-tissue base and dilated glands embedded in it. The developing ovum attaches itself to this layer.

At this period the spongy layer is capable of growing around any foreign substance embedded in it, i.e., of forming a decidual membrane.

After its descent from the fallopian tube into the uterus the developing ovum is implanted in the mucosa. The fertilized ovum implants itself because the outer blastular cells dissolve and destroy the slack epithelial uterine coat.

First the ovum submerges into the compact layer, then the uterine mucosa begins to grow thicker and considerable changes in the decidual membrane take place.

This membrane, expelled with the foetus during parturition, is divided into the *decidua parietalis*, the *s. vera* which lines the entire surface of the uterus not occupied by the ovum, the ***decidua capsularis***, the ***s. reflexa*** which covers the ovum from the side of the uterine cavity, and the ***decidua basalis*** which attaches the ovum to the wall of the uterus.

The maternal part of the placenta forms from the ***decidua basalis***.

The outermost layer of the dividing ovum (trophoblast) forms numerous villi which are subsequently penetrated by foetal blood vessels originating from the mesoblast. The villi of the villous foetal membrane (***chorion***) grow into the enlarged venous spaces (***lacunae***) of the basal membrane, which ensures the nutrition of the embryo from the maternal blood. In man the villi of the foetal chorion are directly immersed in the maternal blood lacunae. The foetal blood is therefore separated from the maternal blood only by a double layer of epithelium which covers each villus (hemochorionic placenta).

At the earliest stages of its development the ovum receives its nourishment from the surrounding fluid (in the uterus it is the secretion of the uterine glands). Later it is nourished from the yolk sac in which the first blood vessels *vasa omphalo-mesenterica* are formed. In man, this source of nourishment plays an insignificant role.

The placenta is the organ through which the foetus respires and is nourished. Blood passes from the foetus to the placenta along the umbilical arteries and returns along the umbilical vein. The processes of nutrition, respiration and excretion take place in the lacunae of the placenta. It has also been found recently that the mother and foetus are connected through the nerve endings in the uterus and the afferent fibres which extend from them. For example, stimulation of the foetal skin produces reflex changes in the mother's respiration and blood pressure. This is connected with the fact that the sex hormones act upon the afferent systems of the uterus and modify the sensitivity of the receptors situated in its walls. Phenomena indicating that the respiration and blood circulation of the mother vary with the changes in the oxygen content in the uterine blood vessels are also observed.

Considerable amounts of oestrogens are formed in the placenta; they cannot be formed in the ovary owing to discontinued development of follicles during pregnancy. In addition, the placenta forms chorionic gonadotropin whose biological action is somewhat similar to that of the gonadotropic hormones of the hypophysis; large amounts of it are excreted with the urine. The placenta also elaborates progesterone contained in the urine as its degradation product—pregnanediol which can be determined by physicochemical methods.

The process of the passage of nutritive substances from the mother's organism into that of the foetus is hardly known. The epithelium which covers the villi plays an important part in this process. It will be observed that in the first place it is the amount of blood flowing through the uterine vessels which rapidly increases during pregnancy. At the initial stage of pregnancy, when the embryos are still small, this is quite sufficient for an ample supply of blood to the placenta. With the progress of pregnancy and the growth of the foetus, these relationships are deranged, since the supply of blood to the uterus does not increase any more. This impedes the gaseous exchange between the mother and the foetus. Suffice it to point out that the oxygen tension in the blood of the intervillous space equals about 60 mm. Hg instead of usual 100 mm. Hg in the alveolar air. This is largely compensated by the different capacities of the maternal and foetal blood to take up oxygen. The dissociation curve of foetal oxyhaemoglobin is shifted to the left compared with that of the maternal oxyhaemoglobin; this means that the foetal blood takes up oxygen more intensively at relatively low partial pressures of the latter. The products of nitrogen metabolism are excreted through the placenta, although a more mature foetus already shows secretion of urine. The digestive apparatus of the foetus is fully formed by the end of pregnancy. Of the enzymes it is pepsin and trypsinogen which are elaborated, while the wall of the intestinal canal contains secretin. Amylolytic enzymes are absent. The liver secretes bile which is accumulated in the intestinal canal in the form of primary faeces or meconium.

Circulation in the foetus is characterized from the middle of intrauterine life by certain features primarily connected with the necessity of supplying arterialized blood to the rapidly growing brain. This arterialized blood, oxygenated in the lacunae of the placenta, flows along the umbilical vein directly to the liver, traverses its capillaries and partly the ductus venosus, passes into the inferior vena cava and is thus carried to the right auricle. From here it is directed through the foramen ovale into the left atrium and left ventricle, and subsequently through the aorta into the system of the future systemic circuit. In the inferior vena cava the arterialized blood of the umbilical vein is mixed with the venous blood which flows from the lower part of the trunk and limbs. In this mixture, however, arterialized blood predominates. Venous blood from the head and upper limbs flows to the right ventricle, but only a small part of it passes through the lung, the greater part traversing Botallo's duct to the aorta. From here the blood flows to the lower limbs, the lower part of the trunk and to the placenta along the umbilical arteries. This blood displacement both in the system of the lower part of the body and in the umbilical arteries is effected by the right ventricle which, consequently, plays an exceptional role in foetal circulation.

From the moment of birth pulmonary respiration and the opening of the pulmonary capillaries enable the blood to flow through the lungs. Botallo's duct and the ductus venosus become desolated. Increased pressure in the left atrium due to its filling with blood closes the foramen ovale. The blood circulation characteristic of the postnatal period of life thus comes into being. The growth of endothelium of the aforesaid blood vessels functioning in the embryonal period leads to their final desolation and obliteration.

Reflex activity of the foetus. Reflex activity in the intra-uterine period is characterized at its early stage by successive phases of development in the course of which both local reflex movements and generalized responses of the muscles of the trunk and limbs are observed.

The first reflex movements of the foetus are those of the head and upper limbs. These are followed by a generalized reaction to stimulations which shows that excitation is easily irradiated in the central nervous system. At first this generalized reaction bears the character of transient muscular contractions, but is later succeeded by contractions of a longer duration. Segment reflex reactions and specialized muscular responses of the trunk and limbs begin to develop only after this stage of generalized reactions. In the embryonal period muscular responses are still inadequate for any complex purposive movements. By the time of birth most mammals and man therefore have very few well-developed reflexes; these are of biological importance, i.e., they ensure the conditions necessary for the existence of the newborn. These highly important reflexes are the respiratory, the suckling, coughing, vomiting and vocal reflexes. It will be observed that the suckling reflex is very complex already by the time of birth. The suckling movements of a newborn child, which has never taken any food before, considerably intensify metabolism and reduce the content of blood sugar. Thus, the entire chain of reactions, connected with feeding and subsequently largely governed by conditioned-reflex activity are already in evidence. It is the low content of blood sugar which causes the unfed newborn child to cry. The child's cry constitutes a very important reaction to stimulations coming mainly from the internal environment. Despite the slightly developed exteroceptive connections at the time of birth, the newborn child exhibits complex interoceptive reflexes which determine its principal reactions in the first hours and even days of life. The exteroceptive reflexes form only during postnatal development.

Parturition

During the greater part of pregnancy the smooth muscles of the uterus produce only inconsiderable rhythmic contractions which intensify the blood circulation in this organ. As the muscle fibres of the uterus stretch (due to the growth of the foetus), their excitability increases. During the last days of pregnancy the contractions of the uterus become more powerful. At the same time the position of the foetus changes and the muscles of the cervix uteri stretch.

Actual parturition consists of a series of successive uterine contractions which are primarily designed to dilate the cervix uteri (the first stage of labour—period of dilatation). During this period the contraction of the longitudinal muscle fibres of the uterus dilates the cervical sphincter. The dilatation is also stimulated by a forcing of the foetal bag, filled during uterine contractions with amniotic fluid, into the cervical canal. This period terminates by the opening of the uterine cervix and in normal parturition, by the entrance of the foetal head into the pelvis.

The second period, or the period of expulsion, is characterized by more frequent and prolonged contractions of the uterine muscles attended by contractions of the striated abdominal muscles. The diaphragm contracts at the same time and a general increase in pressure in the abdominal cavity results. This increased pressure and contractions of the uterus expel the foetus through the opening of the pelvis and the vagina.

The third, postnatal, period which usually begins 20 to 30 minutes after the birth of the child is characterized by the contraction of the uterus and expulsion of the placenta and decidual membranes.

Parturition is connected with a number of changes taking place in the organism at the end of pregnancy. They include, first of all, the mechanical stimulation of the uterine baro- and mechanoreceptors by the growing size of the foetus. Then there is an increase in the content of oestrogens in the blood which suppress the elaboration of progesterone, the hormone of the corpus luteum. The amount of oxytocin, the hormone secreted by the posterior lobe of the hypophysis and stimulating uterine contractions, is also increased.

The aforesaid increase in the sensitivity of the uterine interoceptors to chemical stimulations produces a greater effect of such products as acetylcholine and oxytocin on the uterine muscle. The still little-known influences exerted by the foetus are, no doubt, very important. They include the growing intensity of the foetal movements in the last period of pregnancy and the effect of the foetus on the uterine interoceptors. The suppression of the corpus luteum or elaboration of progesterone by the placenta and the greater secretion of oestrogens by it, result from changes in the activity of the hypophysis which greatly influences the onset and course of parturition. When labour begins each pang is accompanied by a reflex secretion of oxytocin in the blood.

Transection of the spinal cord in the thoracic region does not markedly influence the course of parturition in dogs, while the destruction of the lumbosacral division of the spinal cord makes parturition altogether impossible. This shows that the unconditioned reflexes directly connected with parturition can be effected through the lumbosacral division of the spinal cord.

There is no doubt that the cerebrospinal coordination of parturition is in its turn influenced by the higher nervous centres and, above all, by the cerebral cortex. A number of stimulations (pain-producing, emotional) are known to influence the course of parturition.

The method of anaesthetization of childbirth widely used in the Soviet Union is based on the action of verbal stimuli on the higher nervous activity involved in pain sensations. The cortical mechanisms regulating parturition are at the same time an important factor by means of which the physician can influence this highly complex physiological process.

Lactation and Regulation of the Activity of the Mammary Glands

Two functions, secretory and motor, are distinguished in the activity of the mammary glands. The first of these functions—lactation—is the process of formation of milk in the glandular tissue. The second function is connected with the expulsion of the milk from the lactiferous ducts. The latter is effected through the contraction of the smooth muscles of the lactiferous ducts penetrating the glandular tissue, and simultaneous relaxation of the smooth muscles of the main duct—the cistern. This reaction of the muscle fibres of the ducts is called the lactation reflex.

The arc of this reflex has been recently investigated; it appears that after transection of the spinal cord in the thoracic region goats lose this reflex.

Studies on goats have shown that the lactation reflex does not disappear after denervation of the nipple. These experiments have established heightened sensitivity of the denervated udder to oxytocin. The arc of the lactation reflex lies in the higher divisions of the central nervous system. Transection of the posterior columns of the spinal cord suspends the motor effect in the activity of the mammary gland, while the secretory effect is retained.

Thus, nervous influences on the mammary glands are exerted along different pathways. The extreme inhibitability of the lactation process itself and its dependence on external stimuli testify to the important, though as yet little-known, role played in this process by the cerebral cortex.

It has lately been possible to elaborate a conditioned reflex to the process of lactation by combining the action of oxytocin with a signalling stimulus—injection of saline and the sound of a bell. These experiments have fully proved the role played by the cerebral cortex in the process of lactation.

Regulation of the secretory activity of the mammary gland involves a special mechanism, whose functioning depends upon influences exerted by the nervous system on the hypophysis and other incretory glands. In 1894, it was shown in Pavlov's laboratory that during pregnancy the mammary glands were enlarged after transection of all nerves leading up to them. It was subsequently found that the state of the mammary glands during pregnancy was closely connected with the function of the ovaries. Their growth in the period of sexual maturation is determined by the action of oestrogens; after early castration the mammary glands do not develop.

Pavlov stressed the importance of studying the nervous influences on lactation. These influences have now been firmly established; they are effected directly through the nervous system and through a neurohumoral mechanism—the hypophyseal hormones whose secretion is regulated reflexly. Data obtained by Pavlov's laboratory show that stimulation of efferent nerve fibres extending to the mammary glands is accompanied by a decrease in lactation and an increased content of solids in the milk. Transection of these nervous pathways prevents this decrease in lactation when pain stimuli are applied, while complete denervation of the mammary gland keeps lactation on low levels. Subsequent researches at Pavlov's laboratory (L. Voskresensky) confirmed that the process of lactation was regulated by nervous mechanism. This mechanism, which governs the work of the mammary gland during lactation, has been recently studied in great detail. Stimulation of the nipples by the young produces reflex secretion of a lactogenic hormone—prolactin—by the hypophysis. If the spinal cord of the rat is transected at a certain level, so that the three posterior pairs of its mammary glands are denervated, and the young is allowed to suckle only these nipples, lactation ceases. But if the young are allowed to suckle the anterior nipples whose innervation is intact, lactation is observed in all the mammary glands. Thus, the hormonal mechanism constitutes an important efferent link of the reflex from the nipples to the mammary gland and regulates the process of milk production. It has been found that both ovarian hormones—oestrogens and progesterone—influence the enlargement of the mammary glands during pregnancy. While the oestrogens stimulate the growth of the lactiferous ducts and the connective tissue, progesterone stimulates the development of the alveoli. Both processes are observed in the course of pregnancy.

Prolactin—a lactogenic hypophyseal hormone—stimulates the development of the mammary gland during pregnancy and after parturition only in combination with progesterone, the hormone of the corpus luteum. The removal of the hypophysis by the end of pregnancy makes lactation impossible, while injection of prolactin induces the resumption of lactation.

The receptive function of the mammary gland is effected by interoceptors situated in the vascular stream, cistern, and small ducts of the glands, and by receptors located in the skin of the nipple.

The foregoing data show the significance the stimulations originating from the gland itself have for its normal activity.

Hereditary Transmission of Acquired Physiological Characters of the Organism

In the course of the animal's individual development the influence of the external environment on the organism leads to an emergence of a number of specific features in its physiological activity. These features include, for example, the relatively well-studied phenomena of muscular training connected with morphological and physiological changes in the muscles, phenomena of adaptation to oxygen deficiency, environmental temperature, food, etc.

According to Pavlov's and Michurin's teachings these changes, closely bound up with the adaptation of the animal to the conditions of the environment, may in a number of cases be transmitted by heredity.

Science still knows relatively few facts of such changes in the hereditary physiological traits of the organism under experimental conditions. But there is a multitude of facts in general biology, livestock-breeding and other branches of practical knowledge which show that some traits acquired by the organism become hereditarily fixed.

Already the experiments of Kammerer showed that the nature of reproduction of the *salamandra maculosa* and *salamandra atra* depended on whether they were kept in a dry or damp environment. For example, when kept in a dry environment, the salamandra maculosa, instead of laying eggs, which is normally the case, retained the eggs in the sexual tracts and gave birth to quite viable larvae. In addition, the colour of the salamandra changed to black. The new phenomena did not fully disappear when the descendants of these salamandras were restored to water. As before, the salamandras did not lay their eggs, while the newborn larvae possessed underdeveloped branchiae. It was similarly possible to modify the process of reproduction of the salamandra atra which normally gives birth to living larvae. In a damp environment it gave birth to larvae with short branchiae. These phenomena were also transmitted by heredity. Kammerer likewise managed to observe the changes in the colouration of the salamandras depending on the background, yellow or black, against which they were kept. These changes in colouration were also transmitted by heredity.

There are indications showing that certain traits of rats (size and chemical composition of muscles) acquired in the process of muscular training are particularly pronounced in the rats of the second and third generations. It has also been demonstrated that if the rat is kept under lowered barometric pressure, a change in the content of oxidative enzymes in its brain results. These changes can be likewise observed in individual animals of the successive generations (E. Kreps).

Investigations conducted on sheep have yielded facts of similar physiological significance. Breeding six generations of European-plains sheep at an altitude of about 2,500 m. above sea level showed that the sheep whose first generations exhibited marked changes in respiration and in the number of erythrocytes at this altitude, subsequently ceased reacting to the oxygen deficiency and no longer differed from sheep long bred in the mountains (R. Olnyanskaya).

Striking, hereditarily fixed modifications of thermoregulation can be observed in the ordinary grey rat *m. decumanus* during the last 50 or 60 years of its penetration to regions lying in different latitudes—from the Arctic to the subtropics.

Thus, the external environment exerts considerable influence on the organism of higher animals, which can be observed in a number of successive generations. This proves Pavlov's views that under certain circumstances conditioned reflexes may become fixed and transmitted by heredity if they are helpful to the given species. Precisely this is responsible for the development of the many aforesaid modifications.

The influence exerted by the environment on the organism at different periods of individual development, as was shown by T. Lysenko on the organisms of plants, is of exceptional importance to this problem as a whole. In this connection it is also important to consider the stages in the development of the animal organism characterized by their different qualitative dependence on environmental conditions.

Stages in the Development of the Animal Organism

The foregoing shows that the process of ontogenetic development of the organism consists of a series of stages characterized, above all, by the peculiar relations between the developing organism and the external environment.

The existence of a fertilized and dividing egg nourished either by diffusion from the surrounding fluid or the yolk sac through blood circulation should be regarded as the first stage in this development. In mammals this stage is very brief; in birds it practically covers the entire embryonal period of development.

The second stage is characterized by nutrition from the maternal organism through the placenta. It is important that influences exerted on the maternal organism at this period may in turn essentially affect the foetus. Soviet scientists have found that if pieces of the white rabbit's ovaries are transplanted to the black rabbit, its impregnation by the white male rabbit produces black offspring. Thus, the maternal medium is responsible for the development of the black colour, although, according to the laws of heredity, the birth of white rabbits should be expected. The influence exerted by the maternal organism is very important at this stage of development.

The third stage in most mammals covers the period from birth to the opening of the eyes. At this stage the young organism cannot yet lead an independent existence, since normal coordination of movements and thermoregulation are still absent, and the gastrointestinal tract is adapted only to nutrition by milk. The conditions of nutrition at this stage of development greatly influence the subsequent period. In man this stage lasts much longer and includes the formation of motor activity and the development of tonic reflexes maintaining the posture of the trunk and the position of the head.

However, at the early age preceding puberty the reactions of the organism to the environment factors greatly differ from those in adults as regards stability of the physiological relations. For example, experiments have shown that mice and field voles do not develop their normal weight and sexual activity if insufficiently fed and watered and kept at high temperatures when young. A subsequent optimal food and temperature regimen fails to restore the deranged functions (body weight, reproductive function). Unfavourable conditions also derange the aforesaid functions in adult animals, but the functions are recovered when normal conditions are restored. Thus, the later stages of ontogenetic development likewise exert an enormous influence on the further development of the organism. At this stage the conditions of the environment determine the viability of the rising generation.

The subsequent stages of development are connected with the emergence of numerous adaptive reactions of the organism aimed at ensuring independent existence in the environment. Although the preceding stages of postnatal development are also connected with the activity of the nervous system, the latter assumes the greatest significance at later periods of development when the formation of the organism is linked up with the emergence of a multitude of conditioned reflexes, which, according to Pavlov, effect the highest equilibration of the animal with the external environment.

PART XII

PHYSIOLOGY OF THE MUSCLES AND NERVES

CHAPTER 47

PHYSIOLOGY OF THE MUSCLES

General Characteristics and Evolution of the Motor Apparatus

The functions of the organism, which have been discussed in the preceding chapters, namely, metabolism, circulation, respiration, digestion and excretion, are usually designated as vegetative functions, according to the terminology introduced by Bichat, the French physician, anatomist and physiologist, at the turn of the 19th century. This designation stresses the fact that the above-mentioned functions relate to the vegetative life of the organism and in their essence are common both to animals and plants. Other functions of the animal organism, which are effected by the skeletal musculature, central nervous system and sense organs and are expressed in movements and sensations not inherent in the vegetable kingdom, are often referred to as animal functions. This division of functions was also connected with the conception of autonomy of the vegetative functions allegedly controlled by a special vegetative nervous system independent of the central nervous system.

At present this contraposition of functions has actually lost its meaning, because in an integral organism, as shown by the investigations of Pavlov and his school, not only the animal but also the vegetative functions are controlled by the central nervous system and by its higher division—the cerebral cortex. The vegetative functions are regulated by the cerebral cortex through the vegetative nervous system, which is under the control of the higher divisions of the central nervous system, rather than through cerebrospinal innervation.

The skeletal muscles of vertebrates normally contract only in response to impulses coming from the central nervous system along the motor nerve fibres. Motor impulses arise in the central nervous system as a result of changes taking place in the external and internal environment of the organism and acting upon its external and internal receptors. Excitation arising in the receptors spreads along the afferent nerve fibres to the central structures where it is transmitted from the afferent to the efferent neuron. The intracentral transmission of excitation involves a series of internuncial neurons.

Thus, the movements of animals are of a reflex nature. I. Sechenov made a great contribution to world physiology when he formulated his proposition that not only the simplest motor reactions of animals, but the most complex manifestations of human behaviour were governed by a reflex mechanism, in the latter case related to the higher levels of the central nervous system ("reflexes of the brain," according to Sechenov's terminology). Sechenov's ideas prompted Pavlov to elaborate his teaching on the higher nervous activity experimentally (Chapter 60).

The connection between the muscular fibres and the nerve cells is formed already at the early stages of phylogenesis of multicellular organisms. Whereas in a primitive unicellular organism the entire protoplasm simultaneously possesses the properties of excitability and contractility, multicellular organisms, in the course of adaptation to the environment and as a result of differentiation and specialization of their cells and tissues, acquire the property of responding to external stimuli by motor reactions through specialized muscle fibres. The muscle fibres are elongated, have a fibrillar structure and are able to shorten.

At low levels of development only part of the cells gives rise to muscle fibres, as for example, the epithelial-muscle cells of the lower Coelenterata. In these cells only the basal part forms an elongated contractile fibre, while the outer part of the cell performs a receptive function. Thus, the same cell discharges integumentary, receptive and contractile functions. But already in higher Coelenterata the functions of reception and contraction are separated. Some of their epithelial cells are supplied by long processes whose end branchings come into contact with the muscle fibres lying deeper (Fig. 183). In other cases (in medusae) between the receptive and the muscle cells there is a network of nerve cells supplied with numerous processes.

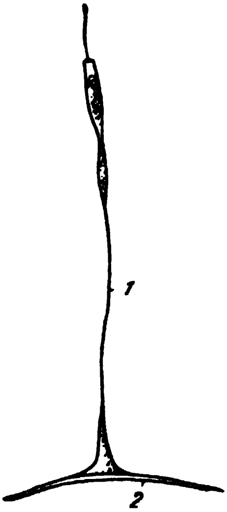


Fig. 183. Myo-epithelial cell of Anemonia sulcata, coral polyp.

1—epithelial cell; 2—muscle fibre.

On higher phylogenetic levels the connection between the receptive structures and the muscles becomes more complicated and is effected through considerable aggregations of nerve cells—ganglia, and in vertebrates through corresponding structures of the spinal cord and brain. In vertebrates the efferent nerve fibres along which impulses are conducted from the central nervous system to the muscles are formed by long processes of the nerve cells (motoneurons) which lie in the anterior horns of the spinal cord. At these stages of phylogenetic development the muscle represents an executive organ in the system of the *motor apparatus* which includes both the peripheral and central nervous links.

Structure and Functional Properties of Muscles

Principal types of muscular tissue. Muscles are divided into two large groups—striated and smooth, according to their structure and function. *Striated muscles* move the extremities and are also called skeletal.* They are formed by fibres of a heterogeneous structure and contract relatively fast. *Smooth* muscles consist of fibres which have a homogeneous structure;

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* The fact that the striated muscles contract in response to impulses from the cerebral cortex gave reason to call them "voluntary" muscles. But since this designation has no physiological meaning and since it may lead to the erroneous conception of indeterminism of the cortical processes, we do not consider it expedient to use this term.

they form the walls of the blood vessels and of the hollow viscera. The contraction of these muscles determines the size of the lumen of the blood vessels and controls the filling and emptying of an organ. Smooth muscles contract slowly, but the contractions may persist for a long time.

The cardiac muscle of vertebrates is of a specific nature. Being striated, it possesses certain functions of the smooth muscle.

First we shall consider the properties of striated muscles.

Structure of muscle fibre. Two kinds of protoplasm are distinguished in the muscle fibre: usual nucleated protoplasm, or *sarcoplasm*, and differentiated protoplasm, or *inoplasm* which has a fibrillar structure. In the course of evolution the undifferentiated protoplasm largely gives way to the fibrillar structure. In the skeletal muscles of vertebrates the sarcoplasm concentrates together with the nuclei at the periphery of the nerve fibre, directly under its sheath, the *sarcolemma*.

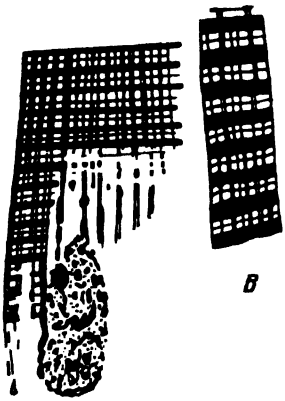

Fig. 184. Structure of striated muscle.

A—myofibrils of human muscle fibre; *B*—bundle of myofibrils (after Lévi).

Owing to the parallel arrangement of the fibrils, the microscope reveals a longitudinal striation of the muscle fibre. In addition, striated muscle fibres show a *transverse striation* because the myofibrils consist of segments which refract light in different ways. Microscopic examination in polarized light shows that each fibril consists of regularly alternating dark and light discs (Fig. 184). The light discs are crossed in the middle by narrow dark stripes. Passing through all the fibrils up to the membrane of the fibre these transverse partitions form the frame of the latter. Owing to these partitions, the discs of all the fibrils (both light and dark) lie on the same level and the transverse striation of the fibre is strongly pronounced. The muscle fibre is divided by these partitions into alternating muscular segments, or sarcomers.

The dark discs belong to anisotropic structures: their physical, particularly, optical and electrical properties (for example, electrical conductivity) differ in the longitudinal and transverse directions. Anisotropy testifies to a regular arrangement of protein molecules in the longitudinal direction. The anisotropy of the dark discs is also manifested in double refraction revealed by examination with a polarizing microscope. The light discs are isotropic and give simple refraction.

The smooth muscle fibres also have an anisotropic substance, but here, unlike the striated fibres, it is distributed evenly. The difference in structure is connected with the functional peculiarities of the principal types of muscular tissue, i.e., with the rapid contractions of the striated muscles and slow contractions of the smooth muscle fibres.

When a muscle contains fibres of both types their functions differ. For example, the muscle which closes the shell in some lamellibranchiate molluscs is made up of two parts, the first consisting of striated fibres and the second of smooth fibres. The contractions of the striated fibres close the shell fast but not firmly. When the shell is to be closed for a longer time (for example, on land) the smooth muscle also contracts and may retain the contraction for many hours.

Certain observations indicate that striation arises simultaneously with the beginning of muscular activity. For example, in a newly hatched fly striation appears after the first flight. Contrariwise, muscles which cease to function or atrophy simultaneously lose their striation. For instance, in certain species of spiders the abdominal muscles of the females long stretched during the maturation of the eggs become inert and lose their striation.

Excitability of the muscle. The basic functional properties of muscle tissue, like those of nervous tissue, include *excitability*, i.e., the ability to develop excitation under the action of certain stimuli. Externally this process of muscular excitation is manifested in its contraction.

Practice shows that muscular contraction which is normally evoked only in a reflex way, i.e., through the central nervous system in response to a stimulation of receptors, can be experimentally induced by direct action of a stimulus on the muscle, as well as by stimulating the motor nerve. Excitation arising as a result of artificial stimulation of this nerve spreads along the nerve and is transmitted from the nerve fibres to the muscle, causing the latter to contract. Muscular contraction is a highly sensitive indicator of the active state of the nerve itself.

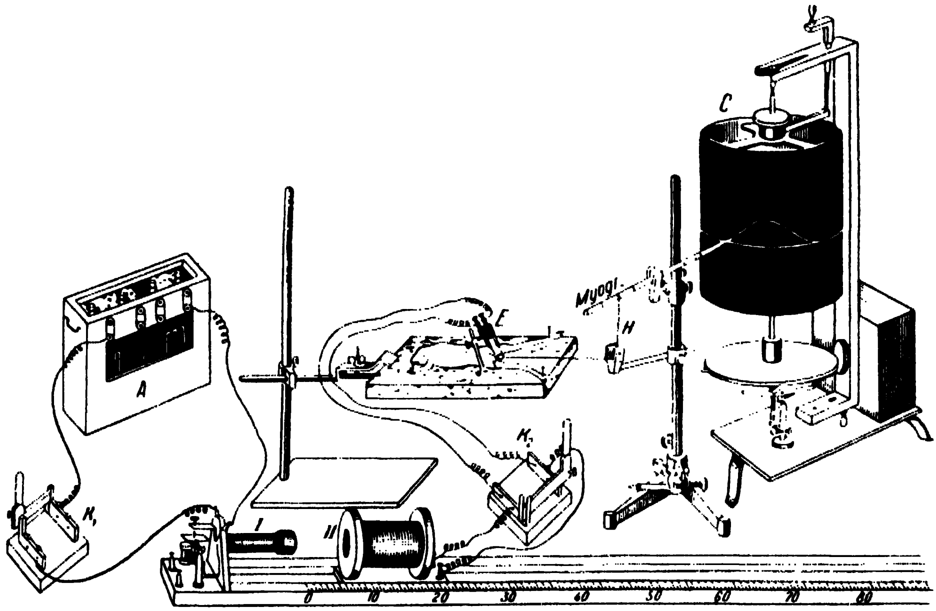

Fig. 185. Installation for electric stimulation of a nerve-muscle preparation.

A—battery; K_1 and K_2—keys; *I* primary and *II*—secondary coils; *E*—electrodes applied to nerve or muscle; *Myogr*—myograph with block *H*; *C*—cylinder of kymograph. Force of stimulation is expressed in centimetres of distance between coils (after I. Beritov).

This makes it possible to study the functional properties both of the muscle and the nerve on so simple an object as a *nerve-muscle preparation* isolated from the body and consisting of a muscle and its nerve trunk. Poikilothermal animals are usually employed for this purpose, since their muscles do not require any special conditions (as regards temperature, oxygen supply, etc.) for the maintenance of their vital activity outside the organism. An isolated nerve-muscle preparation of a frog consisting of the sciatic nerve and gastrocnemius muscle is most frequently used as an object of investigation. In order to prevent such a preparation from drying it is moistened with saline (0.6 per cent solution of NaCl) and placed in a humid chamber.

Various agents may be used for stimulating the nerve and the muscle: mechanical (pricks, strokes, transections), thermal (heating), and chemical (action of acids, alkalis and salts). However, of all the different stimuli it is the electrical which is most extensively applied in experiments (the make and break of a constant current, induction shocks, condenser discharges). The tremendous advantage of electric stimulation consists in the fact that it acts almost instantaneously and permits accurate graduation of the electric current with regard to strength, duration and form. Besides, acting on the tissue for a short time, an electric current of moderate strength does not produce any irreversible changes in it.

Fig. 185 shows an apparatus for the electric stimulation of a nerve-muscle preparation.

The ability of a muscle to react to the stimulation of its motor nerve, i.e., to impulses coming to it from the nerve, is usually designated as *indirect excitability* of the muscle. It should be borne in mind, however, that even when the stimulus acts on the muscle directly, the effect may be due to the stimulation of the motor nerve endings contained in the muscle.

The muscle fibre itself possesses excitability. This can be proved by stimulating those sections of the muscle which do not contain any endings of the motor nerve. Such sections are located in the ends of some muscles (for example, in the *sartorius* muscle of the frog); experiments show that stimulation of these sections results in the contraction of the muscle. Furthermore, it is possible to exclude the influence of nervous elements on the muscle by applying to it some poisonous substances, such as curare. According to the generally accepted point of view, curare paralyzes the endings of the motor nerve in the muscle. In any case when the animal is intoxicated with this poison, the nerve and muscle themselves continue to function, but no excitation is transmitted from the nerve to the muscle; therefore, stimulation of the nerve no longer evokes muscular contraction, though the muscle reacts to a stimulus acting directly upon it.

Such experiments clearly show that the muscle fibres possess so-called *direct excitability*, i.e., ability to react also to stimuli which act directly upon them and not on the nerve fibres.

Excitability is closely connected with another specific property of the muscle—contractility, i.e., ability to change its form in a peculiar way in response to stimulation and to develop mechanical tension. This property of the muscle is dealt with in detail below.

Muscular Contraction

Isometric and isotonic conditions of muscular contraction. During direct or indirect stimulation a muscle shortens or develops tension in the longitudinal direction. This change in the form or tension of the muscle is called *muscular contraction*. If a muscle contracts without lifting any load, it shortens, its diameter increases, but the tension of the muscle fibres does not change. In this case the muscle shortens while the tension remains invariable, owing to which such contraction is called *isotonic* (contraction with invariable tension). If, however, the excited muscle cannot shorten (for example, when its tendons are fixed) the contraction of the muscle is manifested only in the development of tension. Such contraction is called *isometric* (contraction with an invariable length).

In an organism the muscular contractions are never purely isotonic, or purely isometric. The movement of an extremity free from any load comes close to a purely isotonic contraction, while the tension developed in an attempt to lift an excessively heavy load offers an example of almost pure isometric contraction. By increasing the load of the muscle from a minimum to one that the muscle cannot lift it is possible to obtain all the transitional stages—from a purely isotonic to a purely isometric contraction. Modifications in the microscopical picture of the muscle fibre observed during contraction or relaxation of a muscle are shown in Fig. 186.

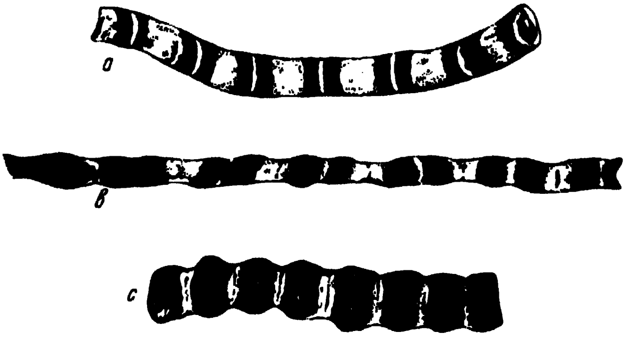

Fig. 186. Change in shape of a striated fibre during contraction. Fibre at rest *(a)*, stretched *(b)* and contracted *(c)* (after Schaeffer).

Two types of recording levers (myographs) are used in analysing muscular contractions graphically. In isotonic recording (Fig. 187) one of the ends of the muscle is fixed, while the other is attached by its tendon to an easily movable lever of the myograph. The end of the lever touches the smoked surface of the paper band of the kymograph and as the cylinder rotates it draws a white line on it.

In isometric recording the free end of the muscle is attached to a tight spring so that the muscle practically retains its length during stimulation.

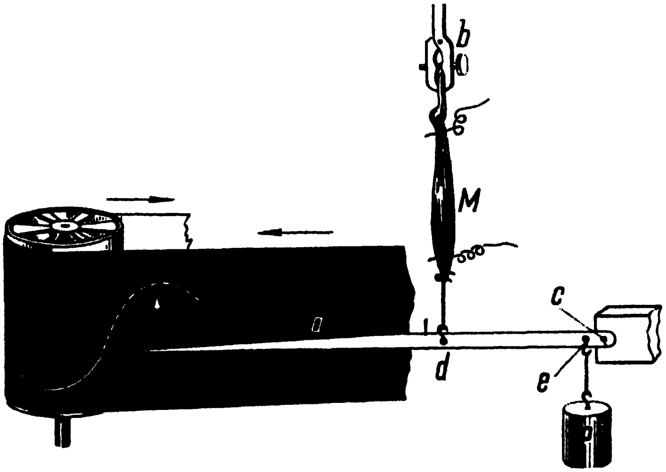

Fig. 187. Recording muscular contraction.

Muscle *(M)*, fastened by clamp *(b)* during contraction raises recording lever *(d)* with load *(p)* suspended from point *(e)* to lever near its fulcrum *(c)*. Free end of lever records curve of muscular contraction on moving band *(a)*.

An insignificant stretch of the spring corresponding to the tension developed by the muscle can be represented on an enlarged scale by means of a long lever attached to the spring or by optical recording. In the latter case a little mirror is attached to the spring; it throws a cone of light onto a band of photosensitive paper moved by the kymograph.

Twitch. If a muscle is subjected to a single transitory stimulation, for example, an induction shock, it reacts with a momentary contraction known as a *twitch*. The contraction curves recorded on the rapidly rotating cylinder of a kymograph under isotonic or isometric conditions have a more or less identical form which is shown in Fig. 188.

Within certain limits the degree of muscular contraction depends on the strength of the stimulation. The minimum strength of stimulation just sufficient to produce an effect is called the *threshold of stimulation*. If the stimulation is intensified above the threshold, the contraction curve increases to a certain maximal value. Stimulation producing the maximal physiological effect is called *maximal stimulation*. An increase in the power of contraction under a submaximal intensification of stimulation is in some measure connected with a gradual increase in the number of the excited fibres. Weak stimulation excites only the most excitable fibres; in maximal contraction all the fibres of which the muscle is made up are affected by excitation. In addition, the degree of contraction of each muscle fibre increases within certain limits when the stimulation is more intense.

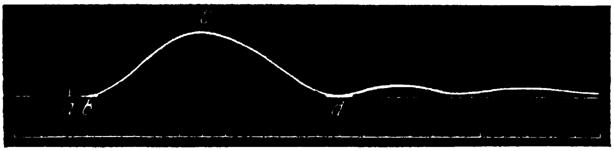

Fig. 188. Curve of single muscle contraction.
a moment of stimulation; *bcd*—curve of contraction. Below—time marked in hundredths of a second.

The curve of a single twitch shows an interval between the moment of application of the stimulus and the onset of the muscular response. This interval is called the latent period of contraction. It usually equals 0.01 second; this is, however, much longer than the actual latent period, since the viscosity and extensibility of the muscle substance retard the beginning of its shortening, while the inertia and friction of the recording lever delay the beginning of the recording. If a muscle is stimulated from the nerve, it is likewise necessary to take into account the time which is required for the conduction of the excitation from the stimulated point of the nerve to the muscle. By using highly sensitive photographic recording it was possible to show that the latent period of contraction of the gastrocnemius muscle in the frog actually lasted about 0.0025 sec. The latent period of contraction covers the initial stage of the excitatory process which is manifested in the modification of the electrical potential in the muscle and precedes the development of mechanical tension (page 505).

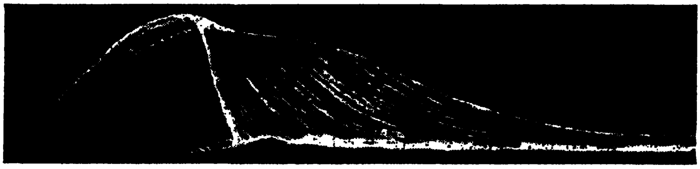

Fig. 189. Effect of fatigue on single muscle contraction (after Waller).

When the tension developed by the muscle suffices to overcome the internal viscosity and inertia of the muscle, the period of shortening begins. In an isolated muscle of the frog it lasts about 0.05 sec. and is succeeded by a period of relaxation lasting about 0.06 sec. Like the shortening of the muscle the relaxation is an active process connected with definite chemical and physicochemical changes in the muscle fibres. A single muscle twitch in the frog is completed in about 0.11 sec.

The period of contraction and especially the phase of relaxation are considerably prolonged when the muscle is fatigued. In this case the relaxation is so retarded that it cannot be completed for many seconds (Fig. 189). This extremely retarded muscular relaxation is called *contracture*.

The duration of a single twitch of the striated muscles greatly differs in various animals. Whereas in some allotherms a muscle contraction may last almost a second, in homoiotherms it lasts in most cases less than 0.1 sec. The wing muscles of some insects contract the quickest: in about 0.003 sec.

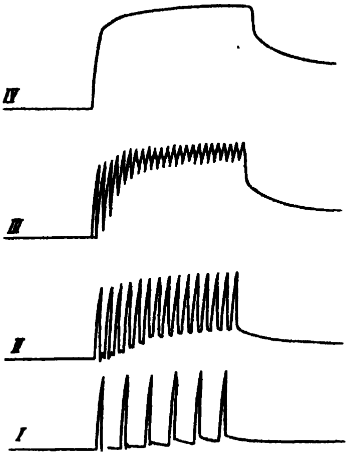

Fig. 190. Different forms of tetanus due to increase in rapidity of stimulation.

ontractions; *II* and *III* effect; *IV*-- full tetanus.

The duration of a single twitch differs in various muscles of the same animal. For example, the latent period and duration of a single twitch in the white muscles of the rabbit are shorter than in the red muscles whose fibres are richer in sarcoplasm and are capable of more protracted tension.

The same muscle, as for example the gastrocnemius in man, often contains both slowly and rapidly contracting fibres. In this case we see two waves on the ascending part of the curve: the first relates to the white fibres and the second, the more delayed, to the red fibres. In the embryo and in the initial period of the animal's postnatal existence the duration of a single muscle twitch is prolonged (Koshtoyants and others). Ontogenetic development is connected with a gradual shortening of the period of a single muscle twitch to the level characteristic of the adult animal.

Tetanic contraction. Normally muscular contractions are relatively long continued. Even the fastest movements performed by man last more than 0.1 sec., while continuous tension of the muscles of the trunk and limbs may persist for many minutes and even hours. The mechanism of continuous contractions called *tetanus* (E. Weber, 1821) was elucidated by a study of muscular contractions occurring in response to a series of stimulations applied successively at short intervals.

If the stimulations are separated by intervals exceeding the duration of a single twitch, the muscle contracts and relaxes between two applications of the stimulus (Fig. 190, *I*).

If the stimuli are applied at sufficiently short intervals, each subsequent stimulus will act on the muscle before the latter is fully relaxed after the preceding contraction. In this case the second, third and all subsequent stimulations will cause the muscle to contract from a somewhat shortened state, rather than relaxed. The curves obtained in this case are shown in Fig. 190, *II-III*. In this figure we see records of incomplete, toothed tetanus. In incomplete tetanus the muscle starts relaxing in the interval between the stimuli, but has no time to relax completely.

If the stimuli follow each other so rapidly that each subsequent stimulus begins to act before the ascending stage of the previous contraction ends, the muscle does not relax in the interval between the stimuli at all. In this case each subsequent stimulation excites the muscle before it begins to relax. This result in complete tetanus is characterized by a complete continuous muscle shortening uninterrupted by relaxations, as shown in Fig. 190, *IV*. The curve of tetanic contraction of a muscle under load is considerably higher than that of a single muscle twitch. Its height increases to a certain extent with the increase in the strength and frequency of stimulation.

Complete tetanus can be attained only at a frequency of stimulation in which the interval between the stimuli is shorter than the phase of development of tension. For example, in a fresh gastrocnemius muscle of the frog in which the phase of progressive contraction lasts about 0.05 sec. complete tetanus can be obtained at a frequency of no less than 20 to 30 stimulations per second. Human muscles and muscles of homoiotherms require more than 30 stimulations per second. The wing muscles of certain insects may show separate contractions even at 300 stimulations per second.

Continuous muscular contraction—tetanus—was regarded as a result of mechanical superposition of individual contractions, invariable in their value, one upon another. It was assumed that at a certain stage of shortening caused by a previous stimulation the muscle contracted in response to a subsequent stimulation as it would contract if it were in a state of rest at the moment of stimulation. This interpretation belongs to Helmholtz (1847), the first to record muscular contractions during single and successive stimulations.

N. Wedensky (1885), a pupil of I. Sechenov, disclosed the inadequacy of this theory of tetanus. He showed that in a rhythmic series of contractions of which tetanus is made up each of these contractions does not remain invariable, but depends on the preceding and influences the subsequent contraction. In the development of tetanic contraction, it is not only the strength of stimulation, but also the intervals between individual stimuli, i.e., their frequency, that are therefore very important. The actual height of tetanus varies within extensive limits depending on the strength and frequency of the stimuli applied. There are *an optimum of strength and a frequency of stimulation* under which tetanus attains its maximum value considerably exceeding that which should be expected under conditions of simple superposition. On the other hand, under excessively strong and frequent stimulations the effect is much lower than should be expected (the *pessimum of strength and frequency of stimulation*).

If each subsequent stimulus is applied at a certain optimal interval after the preceding stimulus, it finds the tissue in a state of heightened reactivity and produces an effect which exceeds the value of the response obtained if the stimulus acts on the tissue when the latter is in a state of rest. As a result, the general value of tetanus proves to be higher than could be expected. This state of heightened reactivity which develops in the tissue some time after the response was named by Wedensky (1906) the *exaltation phase*. The optimal frequency of stimulation, which under maximum physiological strength of stimulation produces tetanus of the greatest height in a fresh gastrocnemius muscle of the frog, is 100 per second. For the skeletal muscles of homoiotherms this optimal frequency is somewhat higher.

The exaltation phase is preceded by a state of lowered reactivity known as the *refractory phase*. The effect produced by stimuli applied at short intervals is therefore lower than should be expected (*relative refractory phase*). But if this interval is less than 0.002 or 0.003 seconds, the second stimulus does not produce any contractile effect whatever (*absolute refractory phase*) and does not add anything to the muscular contraction produced by the first stimulus (Fig. 191). The question of the nature of the refractory phase and of the pessimum will be considered later (in Chapter 50); here it must be pointed out that Wedensky's researches have established the exceptional importance of the intervals between the stimuli for the development of tetanic contraction.

Mechanical changes in the muscle during contraction. In response to stimulation, a muscle either shortens or develops longitudinal tension depending on isometric or isotonic conditions; it does not, however, begin to act along its entire length simultaneously. If a single stimulus is applied to the end of a muscle, contraction begins first in this part and then spreads like a wave from the stimulated part to the others.

The propagation of the wave of contraction along the muscle can be examined with the help of myographs which record the thickening of different portions of the muscle. For this purpose two light levers are placed at a certain distance from each other across a muscle consisting of parallel fibres, for example the sartorius. One end of each lever is fastened on the axis on one side of the muscle with the other end touching the smoked surface of the kymograph band. When a single electric stimulation is applied to one end of the muscle the contraction spreads along the muscle fibres at a certain measurable rate, owing to which the lever situated farther from the site of stimulation begins to plot the curve of muscular thickening somewhat later than the lever situated closer. This delay signifies the time required for the propagation of the contraction wave from one lever to the other.

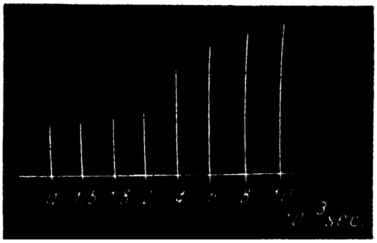

Fig. 191. Influence of length of interval between two single stimulations of skeletal muscle in the frog on force of muscle contraction. First contraction *(a)* was caused by single maximal stimulus; each subsequent contraction was caused by two stimuli divided by interval, the duration of which (in thousandths of a second) is indicated by the figures. If interval exceeds duration of absolute refractory period (beginning with 0.002 second) result is summation of contractions recorded on motionless kymograph drum.

In this way it was established that in the frog's muscle the contraction wave is propagated at the rate of 3 to 4 metres per second; in the muscles of homoiotherms at the rate of about 6 metres per second.

By recording the changes in the thickness of different portions of a muscle it is also possible to trace the influence exerted by the contraction of one section of the muscle on the other sections which are either still at rest or have already returned to rest after contraction. It turns out that in the parts adjacent to the contracted part of the muscle a rise of the curve is preceded by a certain fall of the initial line. This testifies to the fact that the parts still at rest stretch when the adjacent section is contracted. Consequently, along with contractility the muscle possesses the property of ***tensility***. This property may also be observed in an isolated muscle at rest if it is stretched by a load.

At the same time the muscle exhibits the property of elasticity, i.e., the ability to assume its initial form when the forces causing its deformation cease to act. The muscle is considered to have low elasticity when even a small deforming force produces considerable deformation. Elasticity may be perfect or imperfect depending on whether the muscle recovers its initial size completely or incompletely.

If we take a cylindrical bar having length L and cross-section S in which tractive force F causes lengthening a, then, as shown by experiments, $a = \frac{FL}{kS}$, from which it follows that the coefficient of elasticity (Young's modulus) $k = \frac{FL}{aS}$. When k is low, consequently, when the elasticity is at a low level, even slight traction results in considerable lengthening, while the intensification of traction leads to irreversible deformation or rupture of the elastic substance. The following are the coefficients of elasticity and rupture for some organic and inorganic substances (the coefficient of elasticity of the muscle is taken as a unit):

	Coefficient of elasticity (in relative units)	Coefficient of rupture (in kilograms per 1 mm.^{2})
Steel	20,000	20-30
Bone	2,000	10
Lead	1,800	1
Muscle	1	0.5

A living muscle possesses low, but perfect elasticity; even small traction produces considerable lengthening, while the return of the muscle to its initial size, within the limits of reversible deformations, is complete. Only this enables the motor apparatus to recover its initial state after motion. The tendons connecting the muscle with the bone levers also possess perfect elasticity which they retain even after the animal's death, provided they are prevented from desiccation.

There is a marked difference between the elasticity of a resting and an active muscle. This difference is due to an increase in the viscosity of the muscle during contraction. The viscosity conditioned by the friction of moving particles is, in part, responsible that the muscle requires a certain short period of time to resume its initial length.

The animal's death is quite rapidly followed by a rigidity of the muscles (*rigor mortis*); the latter become more elastic, but this elasticity is quite imperfect, and after reaching a certain maximum decreases because of autolysis in the dead muscles.

Absolute muscular strength. The tension developed by a muscle during maximal contraction is the *absolute muscular strength.* It can be measured by the value of the load which must be applied to the muscle fully to prevent its shortening during maximal stimulation. The muscular strength, apparently, depends on the number of fibres and, consequently, on the cross-section of the muscle. To make comparison of various muscles possible, it is also necessary to introduce the concept of *specific muscular strength* which is defined as the quotient of the absolute strength of the given muscle divided by the area of the cross-section of its fibres. It happens that various muscles of vertebrates and invertebrates possess a specific strength which is expressed by values of the same order—several kilograms per 1 cm.^{2}, namely: 4 to 5 kg. for muscles of the Arthropoda; 1.5 to 4 kg. for muscles of the molluscs; 2 to 3 kg. for muscles of the frog; 5 to 8 kg. for human muscles. The smooth muscles are characterized by a lesser specific strength of about 1 kg. per 1 cm.^{2}

In an integral organism the maximal work the motor apparatus can perform is determined by the ability of the motor apparatus, particularly its central innervation link, to do considerable work without developing fatigue, rather than by the absolute strength of the muscle as an executive organ. The greater the work performed in a unit of time, the more rapid the development of fatigue which makes further work impossible. For example, when riding a bicycle a strong man can perform 1,200 kg. of work per minute for many hours, 1,800 kg. per minute for one hour and 2,400 kg. per minute only for several seconds. An athlete can run at a rate of 15 to 18 km. per hour for one to two hours, and at a rate of 30 km. per hour only for 0.5 min. A man can perform work equal to 1.5 h.p. (about 110 kg. per second) but only for several seconds.

The total amount of the hardest physical work performed by man usually does not exceed 100,000 to 200,000 kg. per day.

Energy of Muscular Contraction

Anaerobic processes in the muscle. It was known as early as last century that a muscle could perform work without oxygen. An isolated sartorius muscle of the frog placed in Ringer's solution, fully deprived of oxygen, can produce about 1,500 contractions when stimulated every minute, if its metabolites are removed into the surrounding solution (A. Hill and P. Kupalov). The ability of the muscle to contract in the absence of oxygen shows that it can liberate energy by anaerobic reactions of splitting.

The following anaerobic processes are now known to take place in a resting muscle and greatly to increase during activity:

1) decomposition of glycogen to lactic acid with the liberation of 350 to 500 cal. per gram of lactic acid formed. This process goes through a number of well-studied intermediate stages, treated in biochemistry; interaction of glycogen with phosphoric acid and the formation of hexose-phosphates is a sine qua non of this process; only the latter can be converted into lactic acid with a simultaneous liberation of phosphoric acid;

2) decomposition of creatine phosphoric acid (phosphocreatine) to creatine and phosphoric acid;

3) decomposition of adenosine triphosphoric acid to adenosine diphosphoric and phosphoric acids.

All these reactions are exothermic, due to the action of enzymes and involve no oxygen.

Conversion of glycogen into lactic acid in a working muscle was the first of the aforesaid reactions to be studied. In the absence of oxygen this conversion is the basic result of the chemical processes in the muscle. Only 20 to 25 years ago the decomposition of glycogen to lactic acid was regarded as the only reaction producing energy for muscular activity, while the formation of lactic acid was considered the cause of muscular contraction.

Since then, however, all other aforesaid reactions have been ascertained and, what is particularly important, it has been found that muscular activity is possible anaerobically and involving no decomposition of carbohydrates at all (Lundsgaard). This is attained through poisoning the muscle by iodoacetate (or bromoacetate) acid preventing the possibility of glycolysis. Under these conditions muscular contractions cannot persist long; they cease when the entire creatine phosphate is used up. Thus, disintegration of creatine phosphoric acid can produce the energy necessary to ensure muscular contraction.

In the muscle not poisoned by iodoacetic acid the amount of phosphocreatine hardly decreases, but in the absence of oxygen the muscle accumulates lactic acid. In the muscle poisoned by iodoacetic acid the formation of lactic acid is impossible, and the whole amount of phosphocreatine is consumed. Hence, it can be inferred that decomposition of glycogen to lactic acid ensures the possibility of resynthesis of creatine phosphate from creatine and phosphoric acid.

But disintegration of creatine phosphate is, apparently, not a primary reaction. It can occur only in the presence of adenosine diphosphoric acid to which the phosphate group of creatine phosphate with the creatine split off is transferred.

Thus, the cycle of anaerobic transformations in the muscle may be presented approximately as follows. Decomposition of adenosine triphosphoric acid to adenosine diphosphoric acid and phosphoric acid is the primary stage. This exothermic reaction supplies energy for the muscular contraction. In addition, the formation of adenosine diphosphoric acid makes the decomposition of creatine phosphate possible. The subsequent decomposition of glycogen liberates energy necessary for the restoration of adenosine triphosphoric acid and through it also of phosphocreatine. The final result of the anaerobic cycle is the disappearance of a certain amount of glycogen and emergence of an equivalent amount of lactic acid. The process of muscular contraction itself is not connected with the formation of lactic acid: the decomposition of glycogen takes place some time after the onset of contraction and persists for some time after its cessation.

The anaerobic cycle of transformations is actually much more complicated. Part of the adenylic acid is deamidated and NH_3 and inosine acid are formed; this reaction is, apparently, irreversible. Restoration of phosphocreatine is also incomplete: part of it decomposes irreversibly. But adenylic acid and probably phosphocreatine are formed anew from some still unknown nitrous products.

Oxidative transformations in the muscle. Exhaustion of the stockpile of carbohydrates and accumulation of lactic acid are slower if the muscle works in an atmosphere of oxygen. In the presence of oxygen new reactions occur, oxidation of lactic acid being the most important of them. The study of heat production in the muscle, which prior to this worked under anaerobic conditions, has shown that the amount of heat formed after the admission of oxygen is one-fourth of the amount required to oxidize the entire lactic acid accumulated during the anaerobic phase. It has furthermore been found that in the presence of oxygen only one-fourth to one-fifth of the entire lactic acid formed in the muscle in the absence of oxygen is oxidized with a formation of CO_2 and H_2O. The remaining amount of lactic acid is reduced to glycogen by the liberated energy. This sequence of reactions of anaerobic disintegration and aerobic oxidation connected with the resynthesis of glycogen may be schematically presented as follows:*

anaerobic phase of disintegration		$4 C_6H_{12}O_6 \rightarrow 8 C_3H_6O_3$
aerobic phase of	oxidation	$2 C_3H_6O_3 + 6 O_2 \rightarrow 6 CO_2 + 6 H_2O$
	resynthesis	$6 C_3H_6O_3 \rightarrow 3 C_6H_{12}O_6$

In general, approximately three-fourths of the total carbohydrates decomposed to lactic acid are reduced to glycogen and only one-fourth is oxidized.

Investigations of the last decade have shown that the foregoing scheme does not adequately reflect the importance of the aerobic phase. During oxidative processes inorganic phosphoric acid is intensively drawn into the composition of adenosine triphosphoric acid (approximately three molecules of H_3PO_4 per atom of the oxygen absorbed). The oxidative processes are, thus, connected with processes of phosphorylation.

Carbohydrates are not directly used in muscular contraction, but in restorative processes which make protracted muscular activity possible.

In addition to oxidation of carbohydrates oxidative reactions of other substances (proteins, amino acids, and, probably, fats) may also take place in muscles functioning within the organism and partly in isolated muscles. It has been found that in a muscle poisoned by iodoacetic acid phosphocreatine is partly resynthesized at the expense of some oxidative transformations. Studies of the respiratory quotient (Chapter 34) show that in nonstrenuous human muscular work its value usually lies between 0.8 and 0.9, reaching almost 1.0 in strenuous work. It would therefore be erroneous to assume that in the end, when the muscles are normally supplied with oxygen, they derive all their energy only from the oxidation of carbohydrates. Without oxidation of carbohydrates, however, no normal muscular activity is possible.

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* For the sake of simplicity, the formation of hexose from glycogen, as well as the reactions of phosphorylation, are omitted. The energy of oxidation of lactic acid is not fully utilized for the reduction of glycogen; a considerable part of this energy is expended as heat.

Chemical processes in human muscular activity. The foregoing data on the chemistry of muscular activity, obtained mainly on isolated muscles, warrant important conclusions concerning human muscular activity. The ability of man "urgently" to exert considerable muscular effort testifies to the fact that the energy required for work may be liberated as a result of anaerobic reactions.

Let us consider a simple instance. A man weighing 60 kg. races up a flight of stairs seven metres high in 10 seconds. During this time his leg muscles perform 420 kg. of mechanical work, which is approximately equivalent to one kilo-calory (k.cal.). Since no more than 25 per cent of the entire energy liberated in the muscles is transformed into mechanical work, the total expenditure of energy required for the performance of this work corresponds to 4 kilo-calories. It is known that one litre of oxygen consumed by man liberates approximately 4.8 kilo-calories (details concerning energy exchange may be found in Chapter 34). Hence, in order to make the liberation of 4 kilo-calories in 10 seconds of work possible, the consumption of oxygen by man during this period must amount to about 800 ml. (80 ml. per second). But at rest man consumes approximately 200 ml. of oxygen per minute, or about 3.5 ml. per second. In ten seconds the consumption of oxygen cannot rise from 3.5 to 80 ml. per second, since neither respiration nor the work of the heart, which ensure the supply of oxygen to the muscles, is able substantially to increase in so short a time. It must therefore be admitted that the aforesaid 10-second work could be performed only because muscular contractions are possible at the expense of the energy of anaerobic reactions.

A very rapid increase in oxidative transformations in the muscles is impossible because the blood brings to the *resting* muscles a rather limited amount of oxygen, enough to cover the expenditure of energy at rest. The supply of oxygen to the muscles can increase substantially only with an increase in the amount of blood flowing to the muscles. This requires certain changes in the activity of the entire cardiovascular and respiratory systems: acceleration and intensification of the heart-rate, redistribution of the blood, and—as a sine qua non—increased pulmonary ventilation (or else the blood which flows through the lungs in much greater quantities than at rest will not be fully oxygenated). It requires at least two minutes after the beginning of the work for these changes to occur.

Thus, in considerable muscular work performed in a very short period of time the energy output is ensured mainly by anaerobic reactions. In this case large quantities of products of anaerobic disintegration accumulate and are subsequently oxidized when the supply of oxygen to the muscles increases. In our example of a climb to a height of 7 metres in 10 seconds the total amount of oxygen required for the liberation of 4 kilo-calories amounted to 800 ml., while, say, only 100 ml. was actually consumed during the work. The remaining 700 ml. of oxygen represent the *oxygen debt,* i.e., the amount of oxygen consumed after performance of the strenuous work, over and above the amount of oxygen needed for the organism's normal activity (see page 363). This is accompanied by oxidation of the products of anaerobic metabolism formed during strenuous work.

It may be assumed that mechanical work is always performed at the expense of the energy of adenosine triphosphoric acid. Glycogenolysis and oxidative reactions are prerequisites for the restoration of the adenosine triphosphoric acid consumed during muscular work. The difference in the chemistry of the muscles adequately or inadequately supplied with oxygen is that in the former case the products of anaerobic disintegration are oxidized as soon as they are formed, while in the latter case they accumulate until the supply of oxygen to the muscles reaches the value of the oxygen requirement of the muscles; this value is expressed by the amount of oxygen necessary to oxidize all the products of anaerobic metabolism formed in the muscles.

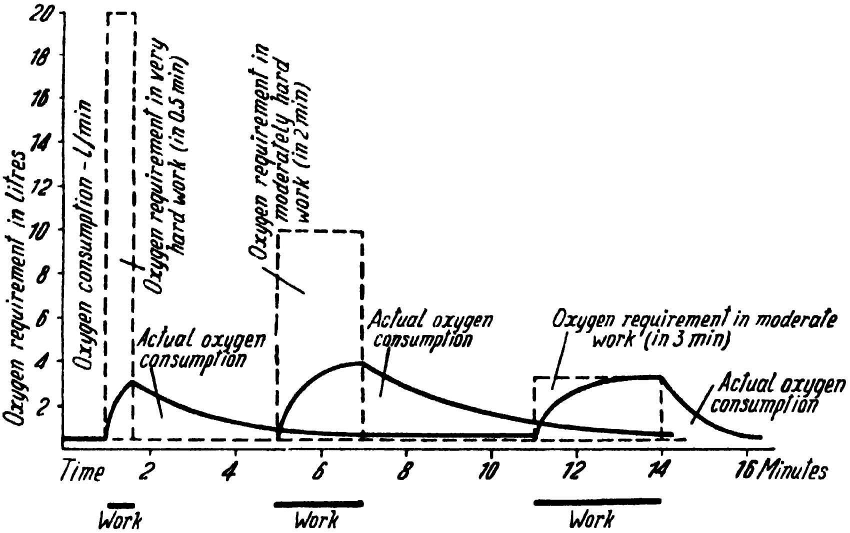

Fig. 192. Diagram of formation of oxygen debt and amount of oxygen required. Rectangles formed by dotted lines show amount of oxygen required in work of different intensity (determined by amount of work done in unit of time). Black lines show actual consumption of oxygen during work (before they cross vertical dotted line delimiting each rectangle on the right) and after work. Horizontal dotted line shows amount of oxygen consumed at rest. Ordinate shows scale of oxygen requirement (in litres) (after A. Hill).

Muscles run up an oxygen debt at the beginning of any more or less strenuous activity. When the amount of oxygen supplied to the muscles per unit of time suffices to oxidize all of the lactic acid formed during that time and the other inadequately oxidized products of anaerobic metabolism, their further accumulation ceases, the products of anaerobic disintegration are removed as fast as they are formed and a so-called "stable" metabolism results (Fig. 192). The excess of products of anaerobic disintegration formed at the initial period of work, when the muscles were supplied less oxygen than they required, may be removed by oxidation after work (payment of the oxygen debt).

After very strenuous and brief work (lasting one or two minutes) the oxygen debt may run into 5 to 10 litres. The content of lactic acid in the blood increases from 0.01 to 0.15 or 0.20 per cent. In the human organism only about one-fourth of the entire amount of lactic acid formed is oxidized to CO_2 and H_2O; the remaining part is converted into carbohydrates. The liver plays an important part in these processes of glycogen resynthesis.

There is no doubt that not only carbohydrates, but also fats and very small amounts of proteins are consumed in the human organism during work. The more strenuous the work, the more carbohydrates are oxidized as compared with fats. During prolonged work (for example, a march of many hours) the stockpile of carbohydrates in the organism sharply decreases and in this case an intake of sugar raises the declining efficiency.

Heat production in muscular contraction. During activity the muscle liberates energy not only in the form of mechanical work: at least 70 per cent of the liberated energy appears as heat. Helmholtz (1848) was the first to observe a rise in temperature in tetanized muscles of the frog by using the thermo-electrical method. But only the studies of the last 30 to 40 years, particularly those of Hill, have made it possible to trace the course of heat production both during tetanic contraction and a single twitch and to compare the heat effect with corresponding chemical transformations in the muscle.

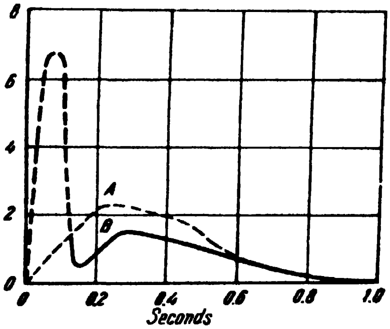

Fig. 193. Curves of initial heat production *(B)* and tension *(A)* of a muscle. Isometric contraction of sartorius in the frog at 0° (after Hartree).

Muscular heat is measured with a thermo-electric battery connected to a sensitive galvanometer. The battery consists of many thermo-elements connected in series. Each thermo-element (thermocouple) represents an electric circuit composed of two heterogeneous metallic conductors soldered together in two spots. When the temperature of both junctions is equal, the circuit does not produce any electric current. But when a temperature difference arises between the two junctions, the galvanometer switched into the circuit reveals the presence of a current, the electromotive force being within certain limits proportional to the difference of temperature between the two junctions. Hill's method is so sensitive that it is possible to record a temperature difference of 0.0000001°.

The process of heat production during a single muscular twitch consists of two phases separated by a certain interval. The first phase is called initial heat production; the second, delayed heat production. *Initial heat* production is similar in aerobic and anaerobic muscular contraction and is, consequently, determined by anaerobic reactions. Under isometric conditions a single twitch of the frog's muscle produces about 0.003 cal. per gram of muscular weight. *Delayed heat production,* which accounts for 60 per cent of the total heat, is observed in the presence of oxygen and persists for a considerable time even after a single twitch. This phase is connected mainly with oxidative transformations.

Initial, i.e., anaerobic, heat production is in its turn characterized by a peculiar distribution in time. A considerable part of the heat is liberated during the development of tension; then the heat production declines and rises again during relaxation. After relaxation 10 to 15 per cent of the entire initial heat is liberated additionally owing to the continued formation of lactic acid from glycogen (Fig. 193).

The relationship of the total heat production to its initial (anaerobic) phase varies with different conditions of aerobic muscular contraction. For example, during single twitches the total heat production exceeds the initial heat production by an average of 70 per cent; during repeated contractions at intervals of one minute, by 90 per cent; and during tetanic contraction, by 2.5 times. This warrants the assumption that during single or infrequent stimulations the contractions are based on a simpler complex of chemical transformations which proceed, probably involving very little or no decomposition of carbohydrates.

It will be observed that not all the heat formed by the muscle can be detected, since certain reactions connected with the recovery of the working capacity of the muscle (resynthesis of adenosine triphosphoric acid, phosphocreatine and glycogen) occur endothermally and thus use up part of the energy liberated during oxidative and other exothermal reactions.

Mechanism of Muscular Contraction

Many physiologists now regard decomposition of adenosine triphosphoric acid as the factor which determines the onset of contraction and supplies the energy for it. The formation of lactic acid ensures only the restoration of the initial organic compounds. The changes occurring during contraction in the anisotropic discs as a result of these chemical transformations are explained by various authors differently: either as a swelling of the anisotropic substance which shortens it, or as an increase in surface tension in the anisotropic discs and in their submicroscopic structures; some authors regard them as coagulation of colloids in the muscle fibre.

Since most organic fibrous substances possess double refraction, it was assumed long ago that the colloidal particles (micelles) of which these substances were composed had a crystalline structure manifested in an orderly, uniform arrangement of the molecules. Subsequent investigations largely confirmed this assumption. As regards striated muscle it was shown that double refraction was inherent in the protein micelles located along the fibre. Myosin, whose solutions possess the property of double refraction, is such a protein in the muscle fibre.

On the basis of these data Meyer (1929) advanced a theory of muscular contraction recently accepted by many physiologists, but not sufficiently substantiated. According to this theory the molecules of the muscle protein (myosin), like many other protein molecules, are long chains of amino acids combined like peptides, i.e., the carboxyl (—COOH) of one amino acid is combined with the amino-group (—NH_2) of another. In the resting muscle the long molecules of myosin are grouped into micelles resembling, as it were, a loose spiral spring. It may be assumed that when the muscle is stimulated the reaction of the medium approaches the isoelectric point of myosin which possesses amphoteric properties; owing to this both positively and negatively charged lateral ion groups are formed. Due to the force of attraction between opposite electric charges the spiral-like threads of myosin contract like spiral springs when the latter are compressed.

If the changes in the shape of protein molecules are to be recognized as the mechanism of contraction and if these changes are directly determined by electric forces of interaction between ion groups with opposite charges, the muscle must be regarded as a sort of electrodynamic mechanism. This conception greatly differs from all previous conceptions that regarded the muscle predominantly as a chemodynamic machine in which chemical energy was transformed directly into mechanical energy.

During the last decade the attention of researchers engaged in the problem of the mechanism of muscular contraction turned to the study of the relation of muscle protein (myosin) to adenosine triphosphoric acid. Changes in the elastic properties of myosin were discovered, i.e., there was an increase in the tensility of the myosin threads connected with the break-up of adenosine triphosphoric acid into adenosine diphosphoric acid and phosphoric acid; it also turned out that myosin was an enzyme splitting adenosine triphosphoric acid (V. Engelhardt and M. Lyubimova, 1939).

According to later data furnished by other authors, it is not myosin that constitutes the contractile substance of the muscle, but actomyosin—a combination of myosin and actin, another muscle protein. In the presence of adenosine triphosphoric acid and potassium ions (in a definite concentration) the threads of actomyosin contract sharply due to a loss of a considerable amount of water.

Fatigue of the Muscle and the Motor Apparatus

If the muscle is repeatedly stimulated at short intervals for a long time, after a number of contractions the height of the latter gradually drops. This drop may reach a point at which the contractile effect fully disappears. When dropping, the contractions grow increasingly longer, especially in their descending phase: when the contraction is over, the muscle does not return to its original length for a long time because it is in a state of so-called contracture (page 466). The latent period of contraction is prolonged, while excitability relatively decreases. The absolute strength of the muscle and the work performed by it diminish. This drop and even full suppression of the functional efficiency of the muscle, which develops as a result of its activity, is called fatigue.

One of the earliest concepts of the mechanism of fatigue was that of inanition of an organ as a result of depletion of working material (Schiff). Subsequently fatigue was interpreted as obstruction of an organ by waste products resulting from metabolism during work (Pflüger). The first cause might hold true only of isolated muscles; experiments show that with a normal blood supply the content of glycogen in a fatigued muscle does not differ much from normal. The accumulation of metabolites (lactic acid, phosphoric acid, etc.) in a working muscle may reduce its working capacity. If a diluted solution of these acids is perfused through the blood vessels of an isolated muscle, the latter shows all the symptoms of fatigue. Contrariwise, transfusion of the muscle with Ringer's solution, which results in the elimination of the waste products, restores the contractile activity of the muscle, although the latter does not receive any new amounts of oxygen or glycogen.

If the activity of the muscle is studied not in isolation, but in connection with the nervous system whence it receives impulses for contraction, it is easy to see that work of the motor apparatus produces fatigue first in its nervous links (the nerve cells, the endings of the motor nerve). During stimulation of the motor nerve, which by its impulses brings the muscle into action, fatigue develops first not in the muscle itself, but in the terminal branches of this nerve.* For example, when the muscle ceases to respond to stimulations applied to the motor nerve through the skin, it still continues to produce considerable contractions in response to stimulations also applied through the skin but to the muscle itself. It will be shown later (Chapter 48) that the nerve fibres themselves are relatively tireless.

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* When a muscle is stimulated from the nerve, phenomena of fatigue should not be confused with those of inhibition (with the pessimum of strength and frequency of stimulation). Phenomena of inhibition develop in the endings of the motor nerve when the latter are sufficiently strongly or frequently stimulated and, unlike fatigue, disappear when the nerve is stimulated less strongly or less frequently (see page 514).

Joint activity of the central and peripheral apparatuses in an integral organism produces fatigue first in the central nervous system. This is revealed, for example, as follows. When the record of human muscular contractions connected with the lifting of a certain load and separated from each other by short intervals exhibits a considerable decline in the contractile effect as a result of the developing fatigue, electric stimulation of the corresponding motor nerve applied at the same intervals continues to evoke a relatively high contractile effect.

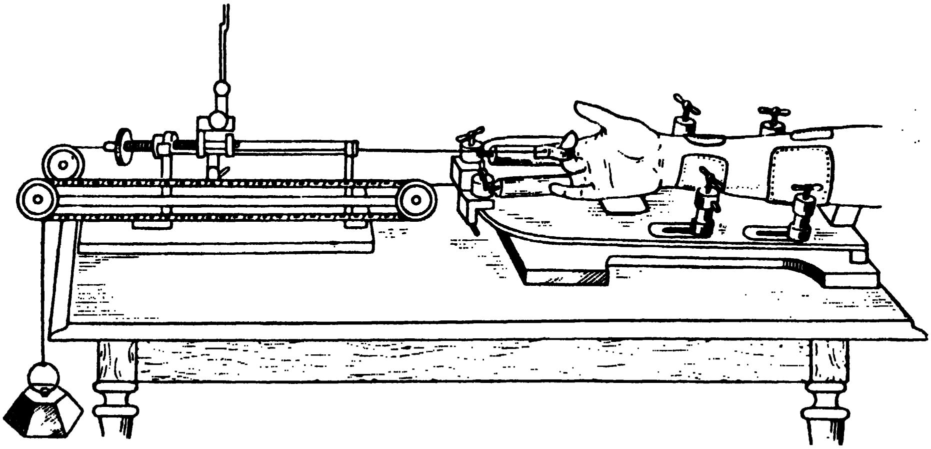

Fig. 194. Mosso's ergograph. Forearm, index and fourth fingers are fixed. By contractions of its flexor middle finger lifts certain load. Movements of finger moving the carriage with the quill are recorded on kymograph band.

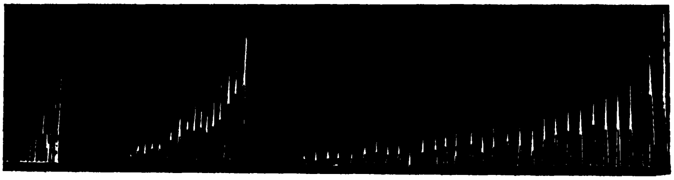

Fig. 195. Ergographic record of onset of fatigue under contractions of various frequency.

1—one contraction per second; *2*—one contraction per two seconds; *3*—one contraction per four seconds. (Read curves right to left).

Phenomena of fatigue developing in man during muscular activity can be investigated with the help of the *ergograph*. A widespread type of this instrument is shown in Fig. 194. With the arm fixed and the adjacent fingers immovable, the flexors of the middle finger lift a certain load. The contraction of the muscles is recorded by a lever on a slowly rotating cylinder. Muscular work can be measured by multiplying the load by the height to which it is lifted. The higher the frequency of contractions, the more rapidly does fatigue develop, everything else being equal (Fig. 195). With a ten-second interval between the contractions and a not-too-heavy load, fatigue may not develop at all.

Using a two-hand ergograph of his own design to study the efficiency of muscles in lifting a load I. Sechenov established a very important fact (1903). Comparing the effect produced by complete rest on the efficiency of the fatigued right hand with that of the rest, accompanied by the work of the left hand, he found that the fatigued right hand recovered its efficiency to a greater extent after *active rest*, i.e., after rest during which the left hand worked; in this case the height to which the load was lifted by the right hand increased more appreciably than after simple rest (see Fig. 242).

A similar effect on the efficiency of a fatigued hand is produced by stimulation of the sensory (afferent) nerves of the other hand by induction current combined with rest, by the work of the legs connected with lifting a load and by any motor activity in general. A temporary rise in efficiency under conditions of active rest is also observed during strenuous activity when fatigue makes further work impossible; a short rest combined with the work of the other hand or with the stimulation of its afferent nerves restores the efficiency of the fatigued hand.

Thus, active rest, accompanied by moderate work of other muscle groups, proves to be a more effective means of fighting fatigue in the motor apparatus than simple rest. These phenomena discovered by Sechenov find practical application in the Soviet system of physical culture.

Sechenov had good reason to connect the cause of the most effective recovery of efficiency in the motor apparatus during active rest with the action of the afferent impulses from the receptors of the muscles, tendons and joints in the working parts of the body on the central nervous system. He considered these stimulative influences on the muscle a reflex act effected through the higher levels of the central nervous system. He also showed that the efficiency of the fatigued right hand likewise increased when the nerves of the left hand were stimulated, while the fatigued hand continued working.

In our time it has been found in the laboratories headed by L. Orbeli that the efficiency of a fatigued skeletal muscle increases after stimulation of the peripheral section of the sympathetic trunk; this is the so-called Orbeli-Ginetsinsky phenomenon (see Fig. 241). This effect is regarded by Orbeli as a manifestation of the specific adaptive-trophic function of the sympathetic nervous system. A comparison of Orbeli's data with the aforesaid investigations of Sechenov leads to the conclusion that normally the sympathetic nervous system is the efferent link by means of which the central nervous system reflexly transmits stimulatory influences to the fatigued muscular groups. This conclusion finds confirmation in the experiments in which the Orbeli-Ginetsinsky phenomenon was reproduced reflexly by various exteroceptive and interoceptive stimulations, the working muscle retaining its connection with the central nervous system only through the fibres of the sympathetic nerve.

The important role played by the higher divisions of the central nervous system, especially the cerebral cortex, in removing the phenomena of fatigue in the motor apparatus is, in part, demonstrated by experiments in which indifferent agents coinciding in time with the action of stimuli that increase the efficiency of the muscles begin to produce the same effect themselves (L. Vasilyev and others).

Functional Properties of Smooth Muscles

In vertebrates smooth muscles are to be found mainly in the viscera and are, therefore, often called visceral. As before stated, their activity manifests itself in slow and prolonged contractions. Both phases of contraction of the smooth muscle are greatly protracted. The latent period of contraction may last for several seconds, and the full period of contraction in response to a transitory stimulation may run into 20 seconds and more (Fig. 196). As a rule, the threshold of stimulation of the smooth muscle is higher than that of skeletal muscle.

In response to repeated stimulations the smooth muscle produces a steady contraction resembling tetanus. Due to the slow character of its contractions, the smooth muscle can be brought into a state of prolonged and persistent contraction by stimulations applied at relatively long intervals. For example, the muscle of the frog's stomach produces a continuous contraction during stimulations applied at intervals of 5 seconds.

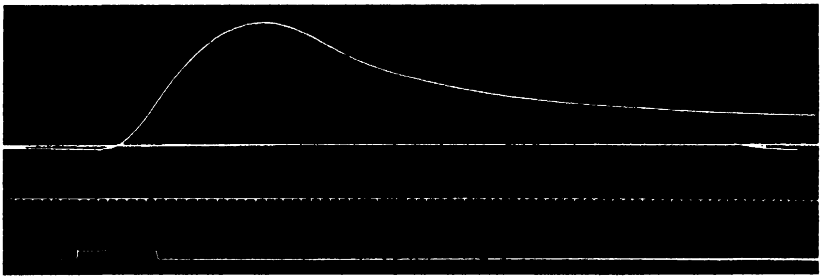

Fig. 196. Contraction of smooth muscle (curve above zero line). Time marked in seconds; stimuli shown on bottom line.

The ability protractedly to maintain a certain level of tension is characteristic of smooth muscle not only in invertebrates, but in higher vertebrates as well. It will be recalled, for example, that the muscles of the arterial walls can remain in a certain state of contraction during the entire life of the organism, thereby keeping the blood pressure on a requisite level. Similarly, the muscles of the stomach and intestinal tract are in a state of at least partial contraction almost during the entire period of digestion.

This form of activity of the smooth muscle is known as tonic tension, or simply *tone*. Its characteristic feature, besides the extremely long and stable effect, is a very low energy output. Should the activity of the smooth muscles require the same energy output as that of the striated muscles, the smooth muscles of the human blood vessels, constituting an inconsiderable part of the entire muscular mass, would alone have to use up at least one-fifth of all the energy normally consumed by the organism. Actually, however, the maintenance of tonic shortening requires but a negligible expenditure of energy, exceeded in tetanic contractions of skeletal muscle by hundreds of times.

An insignificant but obvious increase in metabolism during tonic tensions and a number of other facts suggest the probability that tonic contraction is produced by relatively infrequent impulses (several impulses per second) reaching the muscle asynchronously. Therefore, although separate groups of muscle fibres, each of which is connected with one nerve fibre, produce incomplete tetanus, the general contractile effect of muscle consisting of such numerous groups of fibres appears to be continuous. In this respect the tone of smooth muscle comes close to the tonic tension of skeletal muscle and manifests itself, for example, in the persistence of a certain posture of the animal, by its nature being a weak tetanus produced in individual groups of fibres by reflex excitation.

Mechanism of Movements in Man

The bone levers. Skeletal muscles are attached to the bones by tendons; in movements the bones play the role of levers. More often they are levers of the third order, since the point of application of power (point of attachment of the muscle) is between the point of support (joint) and the point of resistance (for example, of a load at the free end of the bone). The elbow, shoulder and knee articulations offer examples of such levers. As a rule the point of attachment of the muscle is in these cases near the point of support, owing to which even feeble contractions of the muscles are sufficient to ensure considerable movements of the free end of the bone; overcoming active resistance, however, requires a correspondingly greater output of muscular energy.

Bone levers of the second order are less frequent; here the resistance acts between the joint and the point of attachment of the muscle. The role of such a lever is played, for example, by the foot with a person standing on tiptoes, the ball of the foot serving as a point of support; the tendon of Achilles of the gastrocnemius muscle is the point of application of power; the weight of the whole body communicated to the foot through the tibia forms the resistance which is being overcome. Since the point of application of power here is farther from the point of support than the point of application of the load, the force developed by the muscle is correspondingly smaller than the body weight which it has to overcome.

Lastly, bone levers of the first order, with the point of support between the point of resistance and the point of application of power, are found where the maintenance of equilibrium is required. Such is, for example, the atloido-occipital articulation, where the articulation itself is the point of support, while the anterior part of the skull is the load and the tension of the occipitocervical muscles is the power. The hip-joint and the ankle-joint belong to the same type. The farther the point of application of muscular power from the point of support, the smaller the power required to maintain equilibrium.

Fig. 197. Position of plumb line (arrow) drawn through body's centre of gravity.

The direction of the movements of the bones depends on the form of articular surfaces which determines freedom of movement of the articulated parts. An unconstrained solid body can perform both translational and rotatory movements in three dimensions. Thus, it possesses six degrees of freedom of movement. In joints, however, the fixed position of the bones reduces the freedom of movement, which in no case exceeds three degrees. Joints with three degrees, two degrees and one degree of freedom of movement are therefore distinguished.

One of the joints that possesses three degrees of freedom is the scapulohumeral articulation which allows the shoulder to move in three directions: 1) flexion and extension in the saggital plane; 2) adduction and abduction in the frontal plane, and 3) rotation of the arm on its longitudinal axis. This group of joints also includes the hip-joint and the mandibular articulation which permits the mandible to move upward and downward, right and left, forward and backward.

The joints possessing two degrees of freedom include the humeroradial joint which permits flexion and extension of the forearm and its rotation in relation to the humerus, and the knee-joint which allows flexion and extension and, when the leg is bent, also rotation of the leg in relation to the thigh.

Of the joints which possess one degree of freedom mention can be made of the humero-ulnar articulation and the phalanges of the fingers. Joints which possess more than one degree of freedom are served by different groups of muscles ensuring movement in all directions accessible to the given joint.

Standing. Muscles are required not only to move various parts of the skeleton, but also to maintain body equilibrium as, for example, in upright standing. If the whole body represented a column, immovable in any of its parts, the maintenance of its equilibrium in an upright posture would only require a perpendicular, dropped from the body's centre of gravity, to pass through the supporting plane formed by the feet.

The centres of gravity of separate parts of the body, however, do not lie perpendicularly to the articular points of support; tension of corresponding muscular groups is, therefore, required to maintain these parts in a state of equilibrium. For example, the centre of gravity of the head is situated in front of the centre of the atloido-occipital joint; to fix the head in a vertical position, therefore, requires constant tension of the cervico-occipital muscles. Furthermore, the centre of gravity of the trunk (with the head and arms) passes behind the line which connects both hip-joints. The trunk is prevented from falling backward by the tension of *m. ileopsoas* and partly *m. rectus fermoris*. Finally, a perpendicular dropped from the centre of gravity of the whole body (somewhat below the *promontory*) passes in front of the line which connects both ankle-joints (Fig. 197). Here, too, the body is prevented from falling forward by the contraction of a number of muscles, including the gastrocnemius muscles.

Standing is thus ensured by the continuous activity of a large number of muscles. The fact that they perform considerable work is denoted, for example, by an increase in the gaseous exchange, which in some cases reaches 22 per cent over its volume at rest.

Walking and running. In upright standing a perpendicular, dropped from the general centre of gravity of the human body, crosses the supporting area between the feet. If the body is placed in a position with the centre of gravity over one foot, it becomes possible to lift and move the other leg. It is in this way that the process of walking is normally effected; each leg alternately plays the role of a supporting and of a moving extremity. When one leg supports the trunk, the other is thrown forward, touching the ground first with its heel and then with the entire sole. In straightening, this leg takes over the weight of the forward-moving body. The previously supporting leg leaves the ground, though still touching it with the tip of the foot as the weight of the body shifts to the other leg. As it straightens out, it pushes the body forward and, following the latter, also comes forward in a slightly bent position in order at the next moment to reassume the role of a supporting leg, etc.

Thus, in walking, the trunk rests upon one leg, but there are moments when both feet touch the ground simultaneously. Unlike this, in running the rear leg becomes detached from the ground by a strong extension before the front leg touches the ground, the body suspended for some time in the air. Owing to this, the body has a much greater range of vertical displacements in running than in walking.

CHAPTER 48

PHYSIOLOGY OF THE NERVE

Structure and Function of the Nerves

Nerves are cordlike structures consisting of fibres, each of which is formed by a process (axon) of a nerve cell lying either in the spinal cord and brain, or in special aggregations of nerve cells—the spinal and sympathetic ganglia. The nerve fibres are divided into *afferent* (centripetal, or sensory) and *efferent* (centrifugal, and, in particular, motor), depending on whether impulses are conducted from the peripheral receptor apparatuses to the central nervous system, or from the central nervous system to the effector organs (muscles and glands). Usually the same nerve trunk contains fibres of both kinds (mixed nerves).

The main part of a nerve fibre is formed by the axis-cylinder, or axon, which represents a continuous long process of the nerve cell. This process is surrounded by sheaths together with which it forms the nerve fibre. Depending on the type of the sheaths, the nerve fibres are *myelinated* or *unmyelinated.*

The axis-cylinder consists of neurofibrils which are evenly distributed in the neuroplasm and run along the fibre in the shape of parallel filaments. In a myelinated fibre the axis-cylinder is surrounded by a myelin sheath and externally covered by a neurilemma, or Schwann's sheath. The myelin sheath imparts a characteristic white tint to the fibre; in some places (in the so-called nodes of Ranvier) it is interrupted, and the axis-cylinder is covered only by the neurilemma. In an unmyelinated fibre there is no myelin sheath, while the neurilemma is in most cases retained. Myelinated nerve fibres constitute the bulk of the cerebrospinal nerves. Unmyelinated fibres prevail in invertebrates; in vertebrates it is mainly the postganglionic fibres of the vegetative nervous system and some afferent fibres, such as the fibres of pain sensibility, that are unmyelinated.

According to the prevailing point of view, the neurofibrils play the role of conducting elements. The direct participation of the neurofibrils in the conduction of excitation is testified to both by the continuity of the fibrillar structure along the entire length of the axis-cylinder and by the parallelism between the rate of conduction and the degree of development of the fibrillar structures. There is no sufficient ground, however, to connect the function of conduction exclusively with the neurofibrils and to disregard the role of the interfibrillar neuroplasm. The conduction of excitation can be better explained if we proceed from the interaction between the fibrils and the interfibrillar substance. Moreover, attempts have been made (by Peterfi) to show that in a resting living nerve fibre the fibrillar structure does not appear in the shape of continuous filaments, but reveals the presence of colloidal micelles in the nerve, which are oriented along the length of the nerve and come together during stimulation.

Nor is the role of the myelin sheath quite clear. The most plausible supposition is that the fatty covering somehow ensures a high rate of conduction of nervous impulses by which, generally speaking, the myelinated fibres differ from the unmyelinated fibres. At least observations have been described showing that the rate of conduction in a nerve fibre depends on the electric conductivity of the medium by which it is surrounded. As to the insulating properties of the myelin sheath, they are clearly enough testified to by the fact that electric stimulation acts upon the nerve fibre only in the nodes of Ranvier, i.e., in those sections where the myelin sheath is interrupted.

Fundamental Laws of Nervous Conduction

The conductivity of a nerve, i.e., its ability to transmit excitation, is governed by the following laws.

1. The integrity and physiological continuity of the nerve fibre is an indispensable condition for the conduction of excitation. Not only the transection but the ligature of the nerve, which does not violate its anatomical integrity, makes impossible the conduction of impulses ("law of physiological integrity of the nerve").

2. Excitation spreading along a certain nerve fibre is not transmitted to the adjacent fibres running in the same nerve trunk ("law of isolated conduction"). This property is demonstrated by the possibility of localizing precisely the effect of stimulation of the receptor apparatuses and by the possibility of performing strictly coordinated movements.

3. Each nerve fibre is able to conduct excitation in both directions, i.e., to the centres and from the centres, or centripetally and centrifugally ("law of two-way conduction"). This is proved by the fact (DuBois-Reymond) that the stimulation of the middle part of an excised unmixed nerve

results in electric changes at both ends of the nerve characterizing an active state of the tissue (Chapter 50).

Direct physiological proof of two-way conductivity was obtained by A. Babukhin (1877), a Moscow physiologist and histologist, on the nerve of the electric organ of the Nile sheat-fish (*Malopterurus electricus*). This fish, like other electric fishes, can produce electric discharges in the water and utilize them both for defence and attack. In the sheat-fish the electric organ, which consists of a series of columns divided into alveoli, is located directly under the skin on both sides of the body. Each half of the organ is innervated by a big nerve cell situated in the anterior part of the spinal cord. A nerve extends from the cell to the organ; it is a single nerve fibre which, together with the sheaths, is about one mm. thick. Near the organ the fibre divides into numerous branchings which innervate the individual alveoles of the organ.

Separating the nerve fibre from the nerve cell by transection and removing the middle part of the electric organ, Babukhin stimulated the distal end of some nerve branching isolated and transected beforehand (Fig. 198). The stimulation provoked discharges both in the upper and lower parts of the organ. In an isolated branching excitation apparently spreads in an unusual, centripetal direction and upon reaching the unramified fibre is transmitted to other branchings along which it travels in the centrifugal direction to the electric organ. Such transmission of excitation within the limits of the same axon (the so-called axon-reflex, see page 534) does not contradict the law of isolated conduction, since the latter only states that the nerve fibre as a whole conducts excitation in isolation from the neighbouring fibres of the same nerve trunk.

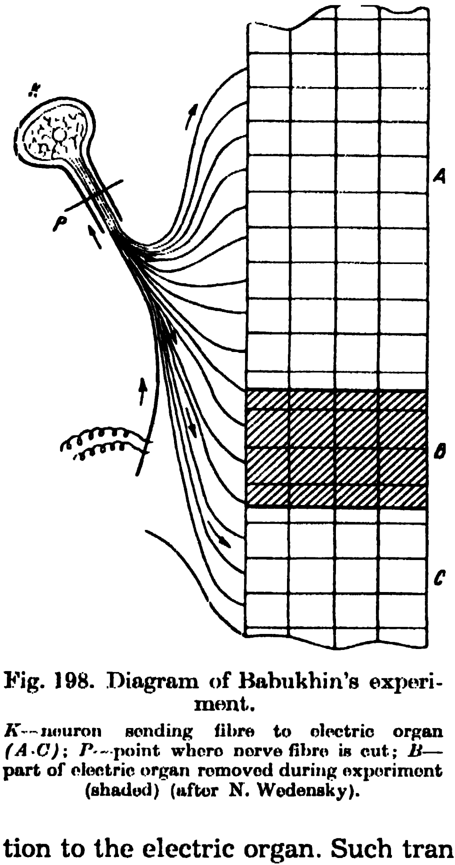

Fig. 198. Diagram of Babukhin's experiment.

K—neuron sending fibre to electric organ (*A*-*C*); *P*—point where nerve fibre is cut; *B*—part of electric organ removed during experiment (shaded) (after N. Wedensky).

Similar proof of the two-way conductivity of the nerve fibre was also obtained by Kühne (1886) on *m. gracilis* of the frog. This muscle can be divided into two parts so that they communicate only by a nerve branching separated from the centres beforehand. It turns out that stimulation of one part of the muscle brings about a contraction also of the other part.

Rate of Conduction of Excitation

Until the middle of last century it was thought that excitation was propagated in a nerve at an extraordinary high speed approaching the velocity of light. The more surprising, therefore, were the results obtained by Helmholtz in measuring this velocity in 1850. By using a very ingenious method of galvanometric measurement of time, Helmholtz found that the velocity of conduction of excitation was actually comparatively low; for the motor nerve of the frog it was only 27 m. per second. Later, Helmholtz demonstrated it by myographically recording two muscular contractions evoked from two points of the nerve located as far apart as possible. The difference between the latent periods of both curves shows the time during which the excitation is propagated between the two stimulated points of the nerve (Fig. 199).

It was subsequently possible to measure the velocity of nervous conduction more accurately by recording electrical changes attending the passage of the nervous impulse in the form of so-called action currents (Chapter 50). This electrographic method is equally applicable to afferent and efferent nerves.

The rate of conduction of impulses varies in different nerves and in different animals. The efferent motor fibres possess the highest conduction rate, the afferent fibres of tactile and thermal sensibility a somewhat lower rate, and the fibres of pain sensibility the lowest rate. For example, the conduction rate in the human motor fibres is from 60 to 120 m. per second; in the fibres connected with pain sensation and in the fibres of the vegetative system this rate is from 1 to 30 m. per second; in thin unmyelinated nerves it is the lowest. In the motor nerves of the frog the conduction rate is approximately 30 m.; in the nerves of the claw of the crawfish, from 6 to 12 m.; and in the nerves of molluscs, from 0.44 to 4 m. per second.

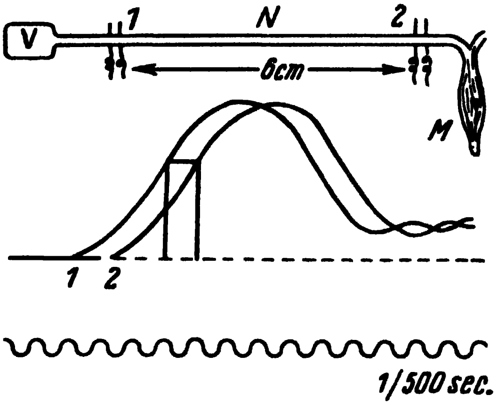

Fig. 199. Two single contractions of the frog's nerve-muscle preparation successively recorded during stimulation of the nerve *(N)* from electrodes located: *1* – near vertebra *(V)* and *2* – near muscle *(M)*.

Difference between latent contraction periods (marked by horizontal line between curves) shows time (0.002 second) it took to propagate excitation along nerve from electrode farthest from muscle *(1)* to that closest to muscle *(2)*; distance between electrodes constitutes 6 cm. (see top of figure). Below – time recorded by tuning fork with 500 oscillations per second. Wave of excitation travelled 6 c [illegible] 1/500 second, he [illegible] elocity of its propagation corresponds to 30 m/sec.

According to observations of a number of authors, there exists a definite dependence between the conduction rate and the diameter of the nerve fibre: thicker fibres possess a greater rate of conduction.

Metabolism and Heat Production in the Nerve

The liberation of energy and metabolism in the nerve fibres are insignificant. They could be investigated only during the last 20 to 30 years. It has been found that a nerve continuously consumes oxygen and liberates CO_2. The respiratory quotient for the nerve of the frog is close to 0.8. This shows that not only carbohydrates are oxidized in the nerve. During excitation of the nerve both the consumption of oxygen and the liberation of CO_2 increase. For instance, at rest the sciatic nerve of the frog liberates 0.008 mg. CO_2 per 1 gr. of the nerve per minute; during artificial stimulation it gives off approximately 16 per cent more. In an anaerobic medium the nerve loses both its excitability and conductivity.

Reversible disintegration of phosphocreatine apparently takes place in the nerve during stimulation: 0.15 mg. of H_3PO_4 per 1 gr. of the nerve is formed as a result of two-hour tetanization. Formation of lactic acid and ammonia in the nerve has also been observed.

Not only metabolism but also heat production increase in the active nerve though considerably less than in the muscle. The passage of one nervous impulse in one nerve fibre over a distance of one cm. causes additional (in comparison with the resting state) liberation of heat which equals to 10^{-12} cal. On the whole active nerve liberates approximately 0.000001 of the energy liberated by the active muscle. Initial and delayed heat production is observed in the nerve, as in the muscle, the former amounting only to one-tenth of the latter.

Relative Indefatigability of the Nerve

The low level of metabolism in the nerve is closely connected with its extremely low fatigability. As shown by N. Wedensky in 1884, a nerve can be continuously stimulated by induction current for many hours without any appreciable weakening of its action on the muscle.

In order to show the tirelessness of the nerve by using muscular contraction as an indicator of its efficiency, it is necessary to safeguard the easily tiring muscle from the continuous action of nervous impulses. For this purpose Wedensky suggested a special method which he named the *method of minimal polarization*. This method is based on the fact that a relatively strong direct (polarizing) current passing through a certain section of the nerve makes it nonconductive (Chapter 49). Protracted action of a strong current, however, leaves a persistent aftereffect in the nerve, and the latter does not recover its conductivity immediately after the current is switched off. Having discovered that the nonconductivity produced by the action of a strong current in a certain section of the nerve can be

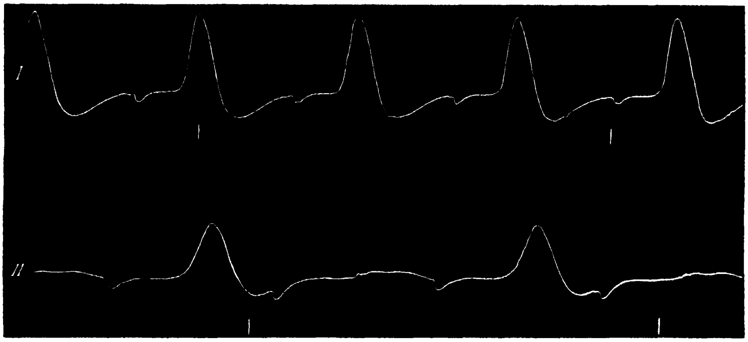

Fig. 200. Changes in action currents of a nerve during its protracted stimulation.

Action currents of the frog's sciatic nerve: *I*—in beginning of stimulation by induction current; *II*—at end of 15-minute stimulation by induction shocks with frequency of 250 per second. Second curve shows considerable drop in amplitude of action currents and 50 per cent diminution in their frequency. Velocity of propagation in nerve diminishes at the same time, which is shown by lengthening of interval between small notch pointed downward (stimulation artefact) and beginning of next action current. Interval between vertical marks corresponds to 0.01 second (after V. Delov).

maintained by increasingly weaker currents, Wedensky proposed to keep up this nonconductivity by a minimal, but still adequate current. By means of a minimal current nonconductivity can be maintained in the nerve for hours; but when the polarizing current is broken the nerve recovers its functional ability at once. This method of temporary exclusion of nervous conductivity is often used in physiological experiments, since it allows rapidly to produce or eliminate nonconductivity in the nerve and to maintain it for a long time, without any marked aftereffects.

Stimulating the proximal part of the nerve by induction current and maintaining nonconductivity in its distal section near the muscle, Wedensky showed that the nerve retained its efficiency even after 9 to 12 hours of continuous stimulation at a frequency of 50 to 100 per second; when the blockade of nervous conduction was removed, the muscle continued to react with tetanic contraction.

In comparison with the muscle and, as we shall see later, in comparison with the nerve cell, the nerve is relatively tireless. This does not mean, however, that there are no modifications in the functional properties of the nerve during its activity. In the first minutes of frequent rhythmic stimulation of the nerve its refractory phase is prolonged (I. Beritov), the heat production per impulse decreases (Hill) and a number of other changes take place, including a decrease in the rate of conduction of impulses. These changes are particularly pronounced when the nerve is stimulated at a relatively high frequency. Fig. 200 shows the fall of the amplitude and the modification of the form of action currents in the nerve as a result of stimulation by induction current at a frequency of 250 per second for 15 minutes.

The functional changes, which under frequent stimulations develop in the nerve quite rapidly during the first minutes of the stimulation, later assume certain stability maintained for many hours.

CHAPTER 49

EXCITABILITY OF NERVES AND MUSCLES

As before stated, both the nerve and the muscle possess the property of direct excitability. But since it is the reaction of the muscle that in most cases serves as an indicator of the active state of the nerve, it is more expedient to study nervous and muscular excitability together. It is possible, of course, to investigate muscular and nervous excitability separately by making use, in the former case, of those sections of the muscle which are deprived of motor innervation and, in the latter case, by taking the corresponding changes in the electric potential as an indicator of nervous excitation (Chapter 50). But such investigation leads to the conclusion that the laws of stimulation are, on the whole, the same in both cases. Since there is no qualitative difference between them, the principal aspects of nervous and muscular excitability can be considered jointly.

As already stated, both objects can be brought into their specific active state by diverse artificial means. But of these means only electric current makes it possible precisely to graduate the strength, duration and form of the stimulating action without causing any irreversible injuries to the tissue. Owing to these properties of electric current, neuromuscular excitability was investigated mainly by the method of electric stimulation.

Polar Action of Electric Current and Electrotonus

Already Volta knew that constant current stimulated a nerve or muscle only at the moments of its make and break. Similar action is produced by rapid intensification or weakening of the current. Moreover, DuBois-Reymond provided a number of facts showing that the stimulating action of electric current at its make or break was connected with opposite poles. But it is mainly Pflüger (1859) to whom physiology owes the knowledge of the fundamental laws governing the action of a constant current upon the nerve and muscular tissues. These include, first of all, the so-called *law of polarity of stimulation*. According to this law:

1) at the make of the stimulating current (or when it is boosted) excitation arises in the region of the negative pole (cathode) and from there spreads to the remaining part of the muscle or nerve;

2) at the break of the current (or when it is weakened) excitation arises in the region of the positive pole (anode);

3) with the same strength of the current the stimulating action at the make of the current is more pronounced than at its break.

The correctness of these propositions can be proved by the following experiments. Stimulation of a very tired or dying muscle produces only local, so-called *idiomuscular* contraction. If such a muscle is stimulated by constant current, it contracts locally at the cathode at the moment of its make, while at the moment of its break it contracts at the anode. In a normal muscle this rule can be proved by recording the propagation of the contraction wave along the muscle.

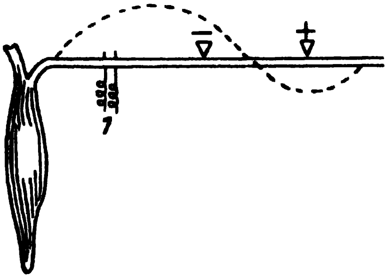

Fig. 201. Electrotonic changes of excitation in nerve.

Triangles marked + and — show location of anode and cathode. Excitation is tested by induction current shocks from electrodes *(1)*. Drop of dotted line below nerve corresponds to drop in excitation (region of anode). Course of this line above nerve marks rise in excitation (region of cathode).

In a nerve the polarity of the emergence of excitation finds expression, for example, in the fact that after ligature of the nerve between the anode and the cathode the muscle contracts only at the make of the current if the cathode is closer to the muscle, or only at the break if the anode is closer to it.

The action of the poles of constant current on nervous and muscular tissues is not confined to a transitory effect in the form of a wave of excitation. When the current passes through tissues, their excitability changes near the electrodes of the constant current.

This can be easily seen when determining the threshold of stimulation by means of electrodes of an induction current before the make of the constant current and during its passage (Fig. 201). Excitability in the region of the cathode is increased, while in the region of the anode it is decreased. These changes in excitability, created by the passage of constant current and described by Pflüger, are called *physiological electrotonus*; it manifests itself either in the form of *catelectrotonus* characterized by heightened excitability and conductivity in the region of the cathode, or as *anelectrotonus* characterized by lowered excitability and conductivity in the region of the anode. The electrotonic changes of excitability spread over some distance both in the extrapolar (beyond the poles of the constant current) and intrapolar (between the poles) areas of the nerve. Between the poles of the current there is an "indifferent point" where excitability remains invariable.

After the break of the constant current transient and less pronounced reverse excitability changes are observed beneath the poles, i.e., a decrease in excitability in the region where the cathode was located and an increase in the former region of the anode.

B. Verigo, Russian physiologist (1883), essentially supplemented these observations of Pflüger; he showed that when a strong constant current passed through the nerve, heightened excitability beneath the cathode was soon succeeded by its decrease and even by complete suppression of excitability and conductivity, i.e., *cathodal depression* developed.

Electrotonic changes in excitability due to the passage of constant current are less pronounced in the muscle than in the nerve and are confined to the narrow region of electrode application.

According to Wedensky's observations (1922), the excitability changes along the nerve during the passage of constant current are not limited to the aforesaid electrotonic regions. Simultaneously, beyond the region of the catelectrotonic increase in excitability the latter decreases, while beyond the region of the anelectrotonic decreased excitability, the latter increases. These reverse changes in excitability observed along the nerve beyond the electrotonic regions Wedensky called *perielectrotonus*;* he designated the diminution of excitability beyond the limits of catelectrotonus as pericatelectrotonus, and the increase in excitability beyond the limits of anelectrotonus as perianelectrotonus. Perielectrotonic changes in excitability are considerably less pronounced than electrotonic changes.

The concepts of perielectrotonic excitability changes, which develop along the nerve, have recently been used by some authors for interpreting the mechanism of protracted, impulseless influences from the nervous centres, transmitted along the nerve; but these authors sometimes overlook the decrement in the propagation of electrotonic and perielectrotonic influences.

The foregoing laws make it possible to elucidate the phenomena observed during stimulation of the nerve by makes and breaks of constant current of different intensities. As should be expected, muscular contraction is observed only at make when a weak current is applied (Table 24). When the current is of moderate intensity, the muscle contracts both at break and make of the current. But when the nerve is stimulated by relatively strong current, contraction is observed either only at break, in ascending current (the anode is closer to the muscle), or only at make, in descending current (the cathode is closer to the muscle).

Table 24

Action of Makes and Breaks of Constant Current of Different Intensities Upon the Nerve

(+ signifies the presence of contraction, — signifies its absence)

Intensity of current	Ascending current (anode is closer to the muscle)		Descending current (cathode is closer to the muscle)	
	Make	Break	Make	Break
Weak	+	—	+	—
Medium	+	+	+	+
Strong	—	+	+	—

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* Peri (the Greek *Περὶ*) means around.

This specific feature characterizing the action of strong currents may have the following explanation. At make of a strong ascending current muscular contractions are absent because the excitation arising beneath the cathode becomes extinguished on its way to the muscle in the region of the anode where excitability and conductivity are suppressed. But at break of a strong descending current the absence of a muscular effect is determined by the fact that the excitation arising beneath the anode is extinguished on its way to the muscle in the region of the cathode where the disappearance of strong catelectrotonus is accompanied by a considerable decrease in excitability and conductivity.

In some cases at make or break of a strong constant current the effect of muscular contraction is not manifested in a single twitch, but in a tetanic contraction, i.e., in *anodal closure* or *anodal opening tetanus.* Observations show that in these cases, too, excitation arises at the cathode when the current is closed and at the anode when it is broken.

The law of polarity is also effective when brief electric shocks act upon the excitable tissue, in particular when these are induction shocks created by interruptions of the current in the circuit of the primary coil. If the passage of the current is very brief, however (in induction shocks it usually constitutes about 0.001 second), excitation arises only at the cathode at the moment the current is boosted. The stimulating action of the anode at the moment the current disappears cannot manifest itself because of the short period of nonexcitability (refractivity) which sets in after the previous excitation.

Polarity of Stimulation of Human Nerves and Muscles

Electrotonic changes in the excitability of the nerves and muscles during the passage of constant current can also be observed in man. For this purpose the electrodes are applied to the skin surface along the course of a nerve, for example the ulnar nerve (*n. ulnaris*) (Fig. 202). The results thus obtained are considerably more complex than in the case of an isolated nerve due to the distribution of the current within the tissues. Upon entering the nerve in the region of the anode (*aa*) the lines of force of the current reduce excitability and upon leaving the nerve in the region of the cathode (cc) increase excitability in this section of the nerve. But not the entire current passes through the nerve. Some of the lines of force leave the nerve near the anode creating here a secondary cathode with a corresponding rise in excitability (cc); contrariwise, some of the lines of force enter the nerve from the surrounding tissues near the cathode thereby anelectrotonically reducing excitability (*aa*). Electrodes of different sizes are ordinarily used with electric current for diagnostic and therapeutic purposes. An electrode with a small surface, or a so-called *active* electrode, is applied to the skin over the nerve or muscle to be stimulated, while

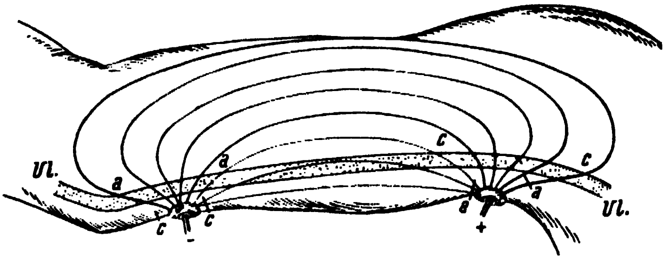

Fig. 202. Diagram of distribution of current lines of force in tissues of the arm during galvanization of ulnar nerve.

the other electrode having a larger surface is applied to a remote part of the body. This method is called ***unipolar stimulation***, since in this case the stimulating effect generally manifests itself only at the active electrode due to the much denser current beneath it.

Depending on whether the *active electrode* is the cathode or anode, cathodal closure and anodal opening contractions are obtained under these conditions according to the law of polarity. In addition, anodal closure and cathodal opening contractions are observed; these are, apparently, conditioned by the action of secondary opposite poles formed near the active electrode. The quantitative correlations between these four kinds of stimulation which were first investigated by Brunner in Petersburg (1862-1863) enabled this scientist to establish a definite law which was called the *electrodiagnostic law of contraction*. If stimulation is begun by a weak current, contraction is obtained only at make of the current when the active electrode is the cathode (cathodal closure contraction—CCC). With a medium current tension anodal closure (ACC) and anodal opening (AOC) contractions are also observed. When strong currents causing pain sensations are applied cathodal opening contraction (COC) is added. In this case instead of cathodal opening contraction cathodal closure tetanus (CCT) is obtained; the latter persists throughout the passage of the current. In accordance with this, the law of contraction can be presented as follows: weak currents—CCC; medium currents—CCC, ACC and AOC; strong currents—CCT, ACC, AOC and COC.

This law is equally applicable to stimulations of nerves and muscles.

Role of the Time Factor in Processes of Stimulation and Excitation

The excitability of various nerves and muscles differs even in the same animal; it varies with the functional state of the tissue. For example, the excitability of a fatigued muscle is lower than that of a fresh muscle.

A simple method of comparative measurement of excitability consists in determining the thresholds of electric stimulation, i.e., in determining the minimal tension or minimal strength of the current at which the effect of excitation first begins to appear. It was pointed out long ago, however, that the stimulating action of the current was determined not only by its tension. For instance, a constant current of moderate tension produces stimulation not only when the circuit is closed or broken, but also as a result of *rapid* alterations of its tension. But if the nerve is stimulated by a current of *slowly* increasing tension, which can be attained by a gradual displacement of the rheochord slider, the current can be considerably boosted and then, also gradually, reduced to zero without causing any muscular contraction. Meanwhile a much weaker current produces maximal effect at instantaneous makes or breaks.

Proceeding from these facts, DuBois-Reymond (1848) formulated his *law of stimulation*, according to which the stimulating action of a current depends not on the absolute value of tension or density of the current but on the rapidity of change in the current: the more rapid this change, the more pronounced the stimulating action of the current.

This law was widely accepted for a long time, but numerous facts that did not fit in with this law were gradually accumulated. These facts clearly showed that when a current was passed through the tissue for a short time, the duration of its action assumed essential importance. Such facts were mentioned already by Fick (1863), Lamansky (1868) and others. Professor I. Shchelkov of Kharkov pointed out in his text-book of physiology in 1871 that for the attainment of a state of excitation in a nerve the current must flow in this nerve for a definite period of time; this period is very insignificant (less than 0.001 second), and it is the shorter, the greater the tension of the current. Shchelkov also indicated that not only a very short electrical stimulus, but also a very rapid mechanical stimulation failed to produce any excitation in the nerve: it is possible rapidly to transect a nerve without producing any contraction in the muscle which is connected with it.

The significance of the time factor is manifested with particular force in slowly reacting tissues, for example, in the smooth muscles of invertebrates and vertebrates. In experiments with stimulating the rabbit's ureter (Engelmann, 1870) by constant current at tensions of 500, 25 and 12 conventional units the minimal duration of the current required to produce a contraction was respectively 0.5, 2 and 4 seconds. In other words, the weaker the stimulating current, the longer must it act upon the tissue to produce a threshold effect of excitation.

B. Verigo (1888) showed that during rhythmic stimulation of a nerve-muscle preparation the development of tetanus required that, in addition to adequate tension and frequency of stimulation, the duration of separate shocks of the current exceed a definite, though very insignificant value (in his experiments it was 0.19 milliseconds at a stimulation frequency of 88 per second).

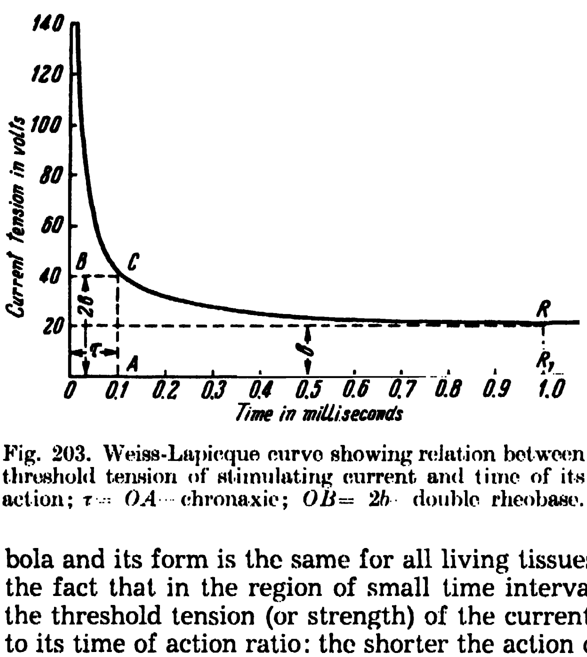

Fig. 203. Weiss-Lapicque curve showing relation between threshold tension of stimulating current and time of its action; $\tau = OA$ — chronaxie; $OB = 2b$ — double rheobase.

If the duration of the current is plotted along the abscissae and the corresponding threshold values of the intensity of the current or voltage along the ordinates, the correlation between these values will be expressed by a curve shown in Fig. 203. This curve approximates to an equilateral hyperbola and its form is the same for all living tissues (Lapicque). It testifies to the fact that in the region of small time intervals (to the left of point *R*) the threshold tension (or strength) of the current is inversely proportional to its time of action ratio: the shorter the action of the current, the greater the tension to produce a threshold effect. But beginning with a certain long duration (to the right of point *R*) the time factor ceases to influence the value of the threshold tension of the current, and the curve runs practically parallel to the abscissae.

The curve shows that each tension of the current has a corresponding minimal time of action on the tissue required to produce excitation.* If at a given tension the time the current passes through the tissue is prolonged above the minimal duration, there will be no change in the onset of the effect of excitation and no second outburst of excitation (unless very high tension is applied). Only that minimal duration will be effective with regard to the development of excitation which at the given tension of the current cannot be reduced without the current losing its stimulating action.

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* In order to determine this duration on the curve, it is necessary to drop a perpendicular from the point of the curve, which corresponds to the given voltage of the current to the abscissae where the duration from the beginning of the action of the current is plotted. The length of the section of the abscissae thus obtained will express the time during which the current of the given tension develops its stimulating action. For example, in Fig. 203 we see that at a tension of 20 V the current must act on a skeletal muscle at least 0.001 second to produce excitation, while at a tension of 40 V 0.0001 second suffices to obtain the same effect.

From the same curve it follows that a minimal tension of the current is required to produce excitation whatever the duration of the currents action. If in this case, for example, the tension of the current is below 20 V, it will produce no excitation whatever the duration of its action. Point *R* on the curve shown in Fig. 203 is, as it were, the critical point: to the left of it any decrease in the duration of the current's action requires an increase in its tension, while to the right of it no increase in the duration of the current's action on the tissue will decrease its tension necessary to produce excitation.

The minimum potential of electric current necessary to produce stimulation is called the *rheobase*. It is the threshold of excitation for a constant current. A current of lower tension does not produce any excitation, no matter how long it acts upon the tissue. But when the tension equals the rheobase, the current can produce an effect only if it acts for a time which corresponds to point *R* on the curve in Fig. 203. The minimal time during which the current of a tension equal to the rheobase must act upon the tissue to produce excitation is called the utilization time of a rheobasic current, or simply *utilization time*. To the right of point *R*, which determines the value of the utilization time, the curve becomes parallel to the abscissae. From that moment on the law of DuBois-Reymond which disregards the significance of the duration of stimulation comes into force.

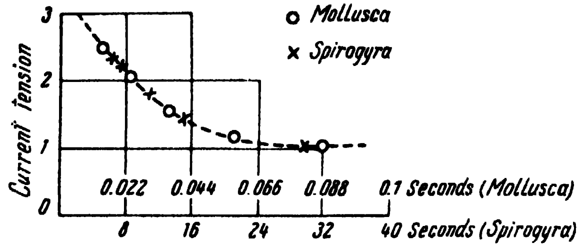

Fig. 204. Curve showing correlation between threshold tension of stimulating current (in volts) and duration of its action for muscle of Mollusca and Spirogyra alga (after Lapicque).

For rapidly reacting skeletal muscles of vertebrates the utilization time is very short. For the sciatic nerve and the gastrocnemius muscle of the frog it is about 0.003 second. Hence it is clear why DuBois-Reymond, who dealt with this object, could not see the dependence between the threshold tension of the current and the duration of its action, since he reduced the duration of the current only to 0.01 second. For slowly reacting muscles the utilization time is hundreds and thousands of times as long.

As before stated, the form of the curve characterizing the excitability of the tissue with regard to the intensity and duration of the stimulus is the same for most diverse tissues. The excitability curve is of the same form for the frog nerve-muscle preparation, for the leg of the snail and for the spirogyra (Fig. 204). It is only the respective absolute values and first of all the duration value which differ: whereas for the skeletal muscle of the frog the utilization time is expressed in thousandths of a second, for the spirogyra it is measured by tenths of a second. These facts lead to the conclusion that the excitability of any tissue is subject to the same law, differing only in its time constant.

The establishment of the foregoing experimental curve, however, requires much time in each case. It was, therefore, important to find a characteristic point on this curve that would allow rapidly and accurately to estimate the "time scale" peculiar to each tissue. This role could be played by the value of the utilization time, but point R, situated in the most gently sloping part of the curve where slight changes along the ordinates are accompanied by considerable changes along the abscissae, cannot be determined with sufficient precision.

On the strength of this, for the purpose of characterizing excitability from the point of view of the time factor, Lapicque proposed to determine the shortest period of time during which a current *double* the rheobase must act upon the tissue to excite contraction. This value was named the *chronaxie*. For each excitable tissue the chronaxie is approximately one-tenth the utilization time (the latter itself, as we have seen, expresses the shortest time during which a current having a potential of *one* rheobase is already able to produce excitation. The chronaxie is usually expressed in thousandths of a second; the rheobase, in volts.

The curve which expresses the correlation between the threshold tension (i) of stimulation and the duration (t) of its action (see Fig. 203) approximates in form, as before stated, to an equilateral hyperbola displaced, in relation to the abscissae, to value b. Weiss, therefore, expressed its equation as follows: $i = \frac{a}{t} + b$, where a and b are two constants. The value of b is easily determined if we take a large-enough t to disregard the value of fraction $\frac{a}{t}$. The equation can then be reduced to $i = b$. Consequently, b expresses the threshold tension of the stimulus when its duration is indefinitely long. As we already know, this is none other than the rheobase. Assuming that in the initial equation i equals $2b$, i.e., a doubled rheobase, it is not difficult to determine the value of the chronaxie (τ), namely: $2b = \frac{a}{\tau} + b$, whence $b = \frac{a}{\tau}$; hence $\tau = \frac{a}{b}$. Thus the chronaxie is expressed by a ratio between the two constants of Weiss's equation. Constant a is of theoretic significance.

Incidentally, Weiss's fundamental equation does not fully conform to the empirically obtained curve which is not a hyperbola in the true sense of the word, since from a certain moment (to the right of point R) it runs parallel to the abscissae, not approximating to it asymptotically as is the case with a real hyperbola. Nor are some other consequences of a hyperbola equation fully confirmed. Determination of the chronaxie as an ***empirical value*** permitting comparison of the rate of development of excitation in various tissues under the same physiological conditions (at a double threshold strength of the stimulus) holds good, however, irrespective of the correctness of the foregoing equation.

The chronaxie is measured as follows. A stimulation of *sufficient duration* is applied, and the threshold of the latter, i.e., the minimal intensity which produces excitation, is determined. This is the rheobase. The threshold voltage thus obtained is doubled, and then the *shortest* duration at which such a current must act upon the tissue to produce excitation is found.

Special devices known as rheotomes are used to close the stimulating current for short intervals varied at will. The general principle of their operation is based on the fact that a certain body (a bullet, the arm of a pendulum, an uncoiled spring, etc.) in its rapid movement successively opens two contacts so connected with the stimulating circuit that the opening of the first turns the current on, while the opening of the second turns it off. If the distance between the contacts and the rate of movement of the body are known, it is not difficult to calculate the duration of the current's action.

This duration can be still easier graduated by means of condenser discharges. Time (t) of the condenser discharge is determined by the following formula: $t = RC \ln n$, where R is the resistance of the circuit (in ohms), C is the capacity of the condenser (in farads) and $\ln n$ is the natural logarithm of the ratio between the initial value of the condenser discharge and its value at the given moment. From this equation it follows that at an invariable resistance of the circuit the duration of the discharge is proportional to the capacity of the condenser. By using condensers of different capacities it is, therefore, possible greatly to vary the duration of the discharge.

A device specially designed to measure the chronaxie of tissues and organs is called a *chronaximeter.*

Expressing the rate of emergence of excitation, the value of chronaxie is connected with the speed of the tissue response in general: as a rule, the more rapid the reaction of the tissue, the shorter its chronaxie. This can be seen from a comparison of the values of the chronaxie and of the duration of contraction in various muscles (Table 25).

Table 25

Tissue	Chronaxie in m/sec.	Duration of muscular contraction (in seconds)
Human skeletal muscles:		
flexors of the arm	0.08-0.16	0.030
extensors of the arm	0.16-0.32	0.040
Frog's sciatic nerve and gastrocnemius muscle	0.3	0.1
Claw muscle of crayfish	11-14	5
Frog's stomach muscle	30-100	15-20

A relation between the value of the chronaxie and the rate of propagation of excitation is also observed: sluggish nerve fibres possess a longer chronaxie. A general rule even has been advanced, according to which the rate of propagation of excitation along the nerve constitutes approximately 1 cm. during the period which equals the chronaxie of the given tissue. For example, in the nerve of the frog with a propagation rate of 30 m. per second and a chronaxie of 0.3 millisecond excitation is really propagated at the rate of about 1 cm. in 0.0003 second.

As a technically convenient method of measuring excitability in relation to the time factor, chronaximetry has been extensively used both in laboratory investigations and clinical practice (Y. Ufland, D. Markov and others) in the last 20 to 25 years.

The theory of chronaxie elucidates the following long-known fact used as an important electrodiagnostic indicator of the reaction of muscular degeneration. At certain stages of degeneration the skeletal muscles first of all lose excitability to induction currents ("*faradic excitability*"), but remain excitable to constant currents ("*galvanic excitability*"). As shown by experiments, in these cases the chronaxie of the muscle considerably increases (by scores and hundreds of times) owing to which transient induction shocks, unlike the more protracted action of a constant current, cannot produce excitation.

The significance of the duration factor in the stimulating action of a current manifests itself with particular force in the fact that alternating currents of high frequency (more than 100,000 periods per second), for example the current of Tesla, pass through the human body without producing any stimulating effect even at high tension, while at the same time an incandescent lamp included into the same circuit begins to glow. The action of high-frequency currents on tissues is confined to thermal effects, which is utilized in electrotherapy for warming up internal organs (diathermia). In this case the duration of each oscillation of the current is apparently insufficient to produce excitation even at a considerable strength of the current.

The significance of the time factor for the development of physiological processes was first disclosed by Wedensky (1892); basing himself on his investigations relating to the role of the strength and frequency of stimulation (Chapter 50), he introduced into physiology the concept of *functional lability* of excitable tissues. By lability Wedensky implied the rate of elementary reactions underlying excitation, i.e., the ability of the tissue to effect a single process of excitation (excitation wave) within a certain period of time. Wedensky determined the value of lability by the maximum number of individual waves of excitation which a living tissue is able to produce per unit of time. As will be shown in Chapter 50, the level of lability and its modification during the functioning of the tissue is one of the main factors which determine the qualitative variety of the reactions of the substratum.

Compared with lability which signifies *the rate of the entire excitation process,* chronaxie which characterizes only *the rate at which excitation emerges,* is, apparently, a more limited and private index. Moreover, measured by the maximum number of waves of excitation that can be produced by the tissue per unit of time, lability characterizes the ability of the tissue to create rhythmic series of these waves which underlie the natural forms of excitation. The rhythmic character of nervous excitation was first proved by Wedensky (1884) in his experiments with the telephonic auscultation of rhythms of excitation in the nerve; these data enabled him to regard lability as the most adequate criterion for characterizing the time factor in the processes of excitation.

Considered from the general biological aspect the value of lability and the value of chronaxie prove to be interconnected, since a rapid process of excitation is usually also characterized by its rapid emergence; contrariwise, a slow process of excitation is usually slow to emerge. The measurement of chronaxie is, therefore, not infrequently used for the purpose of characterizing the lability of certain structures, a low value of chronaxie being taken as an index of high lability and a high value of chronaxie as an index of low lability.

It should be pointed out, however, that when the excitability of the tissue sharply changes as a result of modifications in its functional state, the measurement of chronaxie by the foregoing method does not give an exact idea of the lability change. For example, when the nerve is subjected to the action of agents which lead to a decline in its lability accompanied by a fall of excitability and conductivity, the measurement of chronaxie shows not an increase in its value, as should be expected, but a decrease. A *double high* rheobase can apparently produce excitation in a shorter time than a *double low* rheobase, and, consequently, the doubling of a high rheobase is physiologically not equivalent to that of a low rheobase.

Theories of the Stimulating Action of Electric Current

We have seen that electric current of a certain strength (not below the rheobase) must act upon the tissue for a definite time to produce excitation. We also know that at the make of the current the excitatory process arises in the region of the cathode. The authors of various theories of the stimulating action of electric current proceed precisely from these facts.

In 1896 V. Chagovets, who later became professor at Kiev University, assumed that the stimulating action of electric current on a living tissue was due to the accumulation of positively charged ions at one of the poles, i.e., in the region of the cathode when the current is closed, and in the region of the anode when it is opened.

Proceeding from the assumption that the stimulating action of current depends on the change in the concentration of the salts dissolved in the plasma, Nernst subsequently theoretically deduced a formula expressing the correlation between the strength of the current and the time during which it must act on the tissue to produce excitation. His formula is as follows: $i\sqrt{t} = \text{const.}$, where i is the strength of the current and t is its duration.

But this formula is not applicable to weak currents, since a current weaker than the rheobase does not produce excitation, however its duration t is increased. Being true for "momentary" stimulations, this formula is likewise inapplicable to slowly increasing currents, whose stimulating action is lowered (page 491) owing to a partial reverse diffusion of the ions or to a decrease in the sensitivity of the tissue to the action of these ions (so-called accommodation). Other formulas in somewhat greater accord with most of the observed facts (Weiss, Lapicque et al.) were subsequently advanced.

The formula of Nernst, based on the assumption that the emergence of excitation requires a definite concentration of ions in the region of the cathode of the current acting upon the tissue, does not yet give an answer to the question as to which ions play the principal part in the phenomena of excitation. Chagovets connected the stimulating action of the current with a heightened concentration of hydrogen cations. Loeb (1906) found that a muscle placed in a saline solution preserved its excitability for a long time only if the solution contained univalent (Na, K) and bivalent (Ca, Mg) cations in concentrations (c) which are in a definite correlation. This correlation can be expressed by the following formula: $\frac{c\,(\text{Na, K})}{c\,(\text{Ca, Mg})} = \text{const.}$

In many cases the univalent cations produce a stimulating effect, while the bivalent cations produce a depressive effect.

Proceeding from these data and his own investigations and calculations, P. Lazarev (1916) developed the ion theory of stimulation according to which the stimulating action of a current, when it is closed, is conditioned by a heightened concentration of potassium ions in the region of the cathode.* At the same time an excess of less mobile calcium ions remains in the region of the anode where it reduces the excitability. When the current is opened an opposite picture is observed due to a reverse diffusion of ions. Lazarev extended this theory to other kinds of stimulation—mechanical, thermal and osmotic.

The view that the cathode acts like potassium ions and the anode like calcium ions is supported, in particular, by experiments which show that nonconductivity developing in a certain section of the nerve as a result of its treatment by potassium ions increases when this section is stimulated by the cathode, the negative pole of constant current, and is eliminated by the action of the anode, the positive pole (M. Vinogradov). Contrariwise, the nonconductivity created by treating the nerve with calcium ions increases under the action of the anode and disappears under the action of the cathode of constant current (L. Vasilyev, D. Vorontsov).

The original concepts, according to which the ions are transferred within the field of the electric current, require an essential correction, however, since the latest investigations show that the displacement to which the ions are subjected within the time necessary to produce excitation, does not exceed the diameter of the molecule.

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* It is well known that during the passage of an electric current through a solution of an electrolyte the positively charged ions (cations) are displaced towards the cathode, and the negatively charged ions (anions) towards the anode.

Whereas the theories of Nernst and Lazarev connect the stimulating action of a current on a living tissue with modifications of ion concentration in those sections of the tissue which are situated beneath the electrodes of the acting current, in 1906 Chagovets advanced his condensation theory of excitation based on the phenomena of internal polarization emerging in a living tissue at the make of the stimulating current. From this point of view the area of an excitable tissue, for example of a nerve situated between the electrodes of the acting current, is regarded as a tissue condenser; unlike electrostatic condensers it possesses not an electrostatic but a polarization capacity which manifests its ability to retain the electric charge accumulated during polarization at the poles. When the stimulating current is closed, the condenser is charged in a relatively short time as a result of the developing internal polarization of the tissue, and the positively charged ions (hydrogen ions, according to Chagovets) accumulate in the region of the cathode. Excitation emerges when the charge of the condenser reaches a definite value. When the current is opened a momentary polarization of a reverse direction arises in the tissue, thereby creating conditions for the emergence of excitation in the region of the anode.

Chagovets showed that when the current acted for a very short time, its stimulating action and the internal polarization of a living tissue increased simultaneously and were expressed by the same formulas. As to the displacement of the ions in the electric field of the current, in the given case it is regarded not as the cause of excitation, but as a phenomenon which accompanies excitation when the stimulus acts for a relatively long time.

Chagovets's concepts of tissue condensers found support in the subsequent researches of other authors (Ebbecke et al.). It has been shown that a living tissue is characterized by a certain electric capacity, in this case a polarization capacity, whose value for the nerve trunk of the frog is about 0.01 μF.

V. Pravdich-Neminsky approached the problem of the mechanism governing the stimulating action of a current from another angle. Basing himself on his investigations which revealed the formation of ammonia in the region of the cathode under the action of constant current upon the nerve, Pravdich-Neminsky connected the stimulating action of the current with the breakdown of unstable nitrous compounds in the nerve, while the very propagation of excitation in the nerve he regarded as propagation of an ammoniacal wave. The indubitable value of these researches consists in the fact that they attract the attention of researchers to the problems of biochemical transformations, connected with the emergence and propagation of excitation in a nervous conductor, of which very little is known as yet.

Transmission of Excitation from Nerve to Muscle

Normally the skeletal muscles contract when receiving impulses from the nervous centres along the motor nerve fibres. Each nerve fibre ramifies and innervates from 3 to 160 muscle fibres. A system of muscle fibres innervated by the branchings of one axon and therefore contracting simultaneously forms together with the nerve fibre a so-called *motor unit.*

The morphological connection between the nerve and the muscle fibres is considered by various authors differently: some authors regard the nerve endings only as thickenings, as motor plates; others view them as a fine ramification of nerve fibres coming into direct contact with the modified muscle fibres; still others believe that between the nerve and the muscle there is a new intermediate substance differing both from the nerve and the muscle (receptive substance).

Whatever the ideas of the connection between the nerve and the muscle fibres, it is certain that the area of myoneural junction possesses certain peculiarities with regard to the conduction of excitation compared with the nerve or muscle fibre. As in all other cases when excitation is transmitted from one cell to another, it can spread only in one direction, in this case always from the motor nerve fibre to the muscle fibre. Besides, the conduction of excitation in the intermediate areas is retarded.

As to the mechanism for transmission of excitation from nerve to muscle it was long held that similarly to the transmission of excitation within the nerve and muscle fibres themselves, it was effected by means of an action current. From this point of view the excitation of the muscle arises in response to an electric discharge (action current) in the nerve ending.

Proceeding from these concepts, Lapicque expressed the opinion that impulses could pass from nerve to muscle only if the chronaxie of the nerve and the chronaxie of the muscle were about equal (in any case if one did not exceed the other more than three- or fourfold). Lapicque named this conformity of chronaxies *isochronism*. Derangement of isochronism makes transmission of excitation from nerve to muscle impossible. For example, if the animal is poisoned by curare and the conduction of excitation from nerve to muscle is suppressed, the chronaxie of the muscle is considerably prolonged while the chronaxie of the nerve remains invariable. According to Lapicque, therefore, the previous duration of the action current of the nerve no longer suffices to excite the muscle. There are numerous facts, however, showing that isochronism is not in all cases an indispensable condition for the transmission of impulses from one tissue to another.

A different view on the processes which underlie the transmission of excitation from nerve to muscle has become widespread in the last 20 years. A. Samoilov (1924) was the first to furnish convincing proof that the passage of excitation from nerve to muscle was predominantly a chemical rather than a physical process. With a temperature rise of 10° the rate of transmission of impulses from nerve to muscle in the poikilothermal animal increases, according to Samoilov, on the average by 2.14 times. Such an acceleration of the process as a result of a temperature rise (so-called temperature coefficient) is possible only for chemical reactions and not for physical processes.*

Proceeding from this, Samoilov assumed that the excitation from nerve to muscle was transmitted chemically: the substance educed by the nerve ending stimulated the muscle fibre. He wrote: "...It may be assumed that here, at the border of two cells, one cell educes a certain, as yet unknown, substance and that this substance serves as a stimulating agent for the other cell; this constitutes the passage of excitation from the nerve fibre to the muscle fibre." This may explain both the one-way conduction of excitation in the myoneural area and its lowered rate. Samoilov assumed the existence of a similar mechanism in all cases of transmission of excitation from one cell to another (in particular, from one neuron to another); here, too, in his opinion, transmission was effected by means of a chemical substance possessing a stimulating property.

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* It is well known that at a temperature rise of 10° the rate of chemical reactions increase two- or threefold, while the rate of physical processes increases inconsiderably (about 20 per cent).

In Samoilov's aforesaid experiments the rate of conduction of excitation in a nerve increased on the average by 54 per cent at a temperature rise of 10°. This result shows that in the complex process of propagation of excitation in the nerve chemical and physical components play a certain part, though a considerably lesser part than in transmission of excitation from nerve to muscle.

O. Levi (1921) found that stimulation of the vagus led to formation of a specific substance in the endings of this nerve situated in the cardiac muscle; this substance later proved to be acetylcholine. Numerous further investigations established that this substance was formed in certain links of the vegetative and central nervous systems during transmission of excitation.

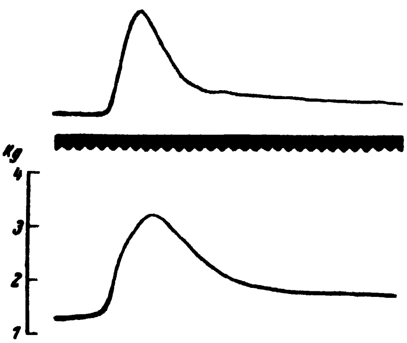

Fig. 205. Lower record—contraction of the cat's skeletal muscle after injection of acetylcholine; upper record—contraction of muscle in response to single nerve stimulation. Ordinate shows scale of tension developed by muscle (in kg.); abscissa shows time (0.01 second).

In the middle of the thirties experiments in which an artificial nutritive fluid was perfused through the blood vessels of a muscle showed that the fluid flowing from the skeletal muscles stimulated through the nerve contained 0.00002 γ* of acetylcholine per impulse of excitation.

It was also shown that a rapid injection of 2 γ of acetylcholine into the artery produced a tetanic muscle contraction (Fig. 205). Very small doses—about 0.000005 γ—were required to excite the muscle fibre when acetylcholine was brought to the region of the nerve ending by means of a micropipette.

In order that formation of acetylcholine cause muscular contraction it is necessary that the amount of this substance formed at each impulse should be fully destroyed during the refractory phase, otherwise the subsequent impulse will not be able to produce excitation. Acetylcholine is split into choline and acetic acid by an enzyme, called cholinesterase. It appears that the concentration of this enzyme in the muscle is highest in the region of the nerve endings.

These facts have led to the hypothesis that the insignificant amounts of acetylcholine formed in the endings of the motor nerve act as intermediaries in the transmission of impulses from nerve to muscle.

Although the participation of chemical processes in the transmission of excitation from nerve to muscle can now hardly be doubted, it cannot be fully accepted that the acetylcholine cycle of biochemical reactions is the only cause of muscular contraction in response to impulses from the motor nerve. The cycle of chemical transformations in this process has not yet been sufficiently studied. There are indications, for example, that an important role is played by adenosine triphosphoric acid, sulphohydrate groups (—SH) and other chemical compounds. It may be assumed that excitation is transmitted by those specific metabolites in the nerve fibre which themselves participate in the cycle of chemical transformations connected with the active state of the muscle.

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* γ signifies 0.001 mg.

CHAPTER 50

THE EXCITATORY PROCESS

Principal Concepts of Electrophysiology

Already in the preceding exposition we frequently referred to electric phenomena in tissues, namely, to electric currents, or potentials,* which are an important indicator of impulses of excitation and warrant a characterization of the excitatory process from the viewpoint of its intensity, duration, rhythm and general nature of its course.

Electric changes in tissues are expressed by insignificant values of energy; for example, in the muscle they are less than 0.00001 of the entire thermal and mechanical energy liberated during contraction. However, the extensive development of electric measuring technique, and in our time also of amplifying devices, has made the electrophysiological method of investigation one of the most perfect and precise methods of studying the dynamics of excitation in the nervous and muscular systems.

The study of electric phenomena in animal tissues began with the discovery made by Galvani, physician and physiologist of Bologna, in 1786. Galvani noticed that when a current between the nerve and the muscle of a prepared leg of the frog was closed with the help of a metallic conductor, the muscle twitched as it did during the passage of a charge from the Leyden jar through it. Galvani interpreted this fact as a manifestation of "animal electricity." He believed that the nerves and muscles were charged with opposite electricity and that in this experiment the metallic conductor only closed the circuit between the nerve and the muscle.

Volta, professor of physics at the University of Pavia and Galvani's contemporary, explained the results of Galvani's experiments by the fact that the metallic conductor used in the experiments was heterogeneous. When the metal came into contact with the humid tissue, there arose a difference of potentials between the metal and the fluid; owing to the heterogeneity of the metallic conductor opposite charges were created at its ends contacting the tissue and produced an electric current.

L. Galvani

Both investigators proved to be right, each in his own way. Galvani found a new variant of this experiment, in which the contraction of the prepared muscle was attained without any metallic conductors, simply by throwing upon the muscle its own nerve (the so-called experiment of contraction without metals). This experiment incontestably proved that an excitable tissue could itself be a source of electricity; it opened a long new chapter of physiology subsequently named electrophysiology.

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* In all cases when *action potentials* are mentioned, it is the *difference of potential* between the excited and the resting sections of the excitable tissue that is implied.

As to Volta, he was the first to discover the source of constant current (the "voltaic pile") in which the potential difference or, in Volta's terminology, the electromotive force resulted from the interaction of the metal and the fluid. The voltaic pile originally consisted of numerous pairs of copper and zinc disks superposed on each other and separated by cloth layers moistened in salt water.* This discovery originated the theory of electric ("galvanic") current and refuted the vitalistic concepts of the specific nature of "animal electricity."

Firm foundations for the experimental study of the bio-electric properties of muscle and nerve were laid in the middle of last century; of particular importance in this respect were the researches of DuBois-Reymond, Hermann, Sechenov and Wedensky who investigated the bio-electric currents by recording them with physical instruments—galvanometers. The use of his telephonic methods (page 503) by Wedensky was particularly fruitful at that stage in the development of electrophysiology.

Currents of rest in muscle and nerve. If the longitudinal surface and a cut end of a muscle or nerve are connected to a sensitive galvanometer by nonpolarizable electrodes (Fig. 206) the galvanometer will reveal the presence of a current which flows in the external circuit from the longitudinal surface of the nerve or muscle to the cut end.** In other words, the cut end of the tissue proves to be electronegative to its longitudinal surface. The current which results from such connection of the longitudinal and transversal surfaces of the tissue was termed by DuBois-Reymond the *current of rest.*

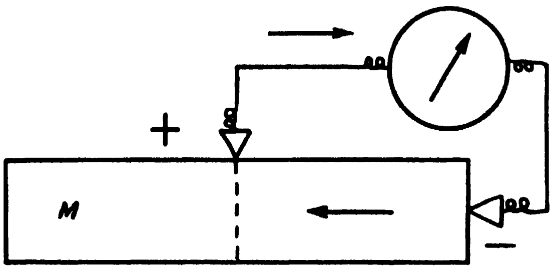

Fig. 206. Current of rest. *M*—muscle (or nerve). Cross-section of muscle (nerve) is negative (—) to uninjured surface (+). Arrows show direction of current in inner and outer circuits.

However, Hermann showed that the emergence of the so-called current of rest was due only to the injury of the tissue, its cause being the difference of potentials between the uninjured part of the tissue (longitudinal surface) and its injured part—the cut end. Thus the current of rest does not pre-exist in the nerve or muscle, as was assumed by DuBois-Reymond, but arises as a result of injuries and, in general, of local alterations in the tissue under various physiological and chemical influences. It was therefore called the *injury current,* or *alteration current.*

It has also turned out that Galvani's experiment with contraction without metals fails if the muscle is prepared very thoroughly, without any injuries. But if the muscle is first injured, the throwing of the nerve upon it invariably produces contraction, when the nerve comes in contact with either the injured or uninjured parts.

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* The most powerful battery of that time consisting of 4,200 pairs of copper and zinc plates was designed in 1802 by the Russian Academician V. Petrov; in addition to the physical investigations which led to the discovery of the electric arc, he carried out a number of experiments connected with the influence of electric currents on aquatic animals.

** As is known from physics, the flow of electricity from the positive to the negative pole is conventionally taken as the course of a current in the external circuit.

The highest difference of potentials, which in the muscle reaches 0.08 V, is observed immediately after the occurrence of the injury. During the first hour the injury current falls almost to half its initial strength. In the nerve the potential difference arising as a result of injury does not usually exceed 0.03 V, and with the lapse of time diminishes more rapidly than in the muscle. In the human nerve it is only about 0.006 V and this is, apparently, due to the abundance of connective tissue layers which represent an accessory make for the current led off from the nerve. As the nerve degenerates the strength of the current, which arises as a result of the injury, gradually decreases; in homoiothermal animals the current fully disappears in 10 days; in poikilothermal animals, in 30 days.

Action current (negative wave of the current of rest). The electric oscillations which accompany the excitatory process in the nerves and muscles are of special interest. Historically the study of these phenomena proceeded from initial observations which showed that the current of rest in muscle or nerve diminished during their stimulation. DuBois-Reymond named this diminution of the current of rest during the active state of the tissue the *negative wave of the current of rest.* In inert galvanometers it appears in the form of a continuous weakening of the current of rest, though in reality it consists of separate rapid oscillations. This was proved by the so-called secondary tetanus. If two nerve-muscle preparations are placed so that the nerve of one preparation lies longitudinally on the muscle of the other, stimulation of the second nerve by induction current leads to a tetanic contraction not only of the second, but also of the first muscle. In this case the nerve of the first preparation is stimulated by a negative wave which accompanies the contraction of the second muscle. But since this stimulation produces tetanus of the first muscle rather than a single twitch, it warrants the conclusion that the stimulus is of an intermittent character.

The phenomenon of the negative wave was interpreted as follows (Hermann, 1867). Just as an injured part of an excitable tissue is electronegative to its uninjured part, any section of the tissue excited at the given moment becomes electronegative to the resting sections. The difference of potentials between an excited and an injured part must therefore be smaller than that between a resting and an injured part. This is what determines the negative wave (i.e., diminution) of the current of rest. The scheme presented in Fig. 206 demonstrates these relationships.

In an excited section electronegativity does not persist long, as is the case with an injured section. Arising for a very short time, it spreads over the tissue together with the excitatory process. The decrease in the potential difference between an injured (permanently negative) and an excited section during the passage of each excitatory wave is therefore very brief (expressed in thousandths of a second). Hermann named these rapid changes of the electric potential in an excited section of a muscle or nerve the *action currents.*

The first proof of the intermittent, oscillatory nature of excitation in a nerve was given by N. Wedensky (1883) who made use of the telephonic method for hearing the action currents of a nerve. By leading off two points of the nerve to a telephone he was able to hear the rhythms of the activity of a nerve under stimulations of different strength and frequency. With the help of this method Wedensky already in the eighties of last century made a number of his fundamental conclusions concerning the rhythms of excitation; these conclusions were subsequently corroborated by other investigators with the help of graphic recording.

Later special galvanometers or electrometers possessing very low inertia of the recording system were used for obtaining graphic records of action currents which usually represent rapid electric oscillations. They include the capillary electrometer, the string galvanometer and oscillographs.

The capillary electrometer consists of a capillary glass tube containing mercury with a weak solution of sulphuric acid above it. At the contact surface of the mercury and acid there arises a difference of potentials, the mercury being charged positively and the acid negatively. The charge reduces the surface tension of the mercury meniscus owing to the mutual repulsion of the charged particles of mercury. If a current is now passed through this system in a direction, for example, that will make the meniscus a cathode and the sulphuric acid an anode, the charge of the meniscus will decrease. Owing to this the surface tension of the mercury will increase and the meniscus will fall being displaced in the direction of the current flow. With a reverse direction of the current an increase in the charge of the meniscus will diminish its surface tension, and the meniscus will rise. Thus the movements of the mercury meniscus are always in the direction of the acting current. These movements can be observed through a microscope, or photographed on photosensitive paper.

The inertia of the mercury meniscus is relatively high, however, and the *string galvanometer* therefore proved to be a better instrument (page 94). In this galvanometer a very thin conducting thread stretched vertically between the poles of an electric magnet can reproduce about 500 oscillations per second without appreciable error.

A considerably higher frequency of oscillations can be reproduced without errors by *loop*, or magneto-electric *oscillographs* which found application in electrophysiology at a later period. The movable system is formed here by a loop of a metallic band stretching from one terminal to the other through a block drawn upward by a spring. The loop is placed between the poles of a permanent magnet. During the passage of the current both halves of the loop are deflected in opposite directions because of the different course of the current in them. This makes the whole loop turn at a certain angle, the value of which is determined by the strength of the current. A beam of light is deflected correspondingly and is reflected by a little mirror fixed on the loop. These deflections of the beams are photographed. Oscillographs of this kind can reproduce about 10,000 oscillations per second without any error.

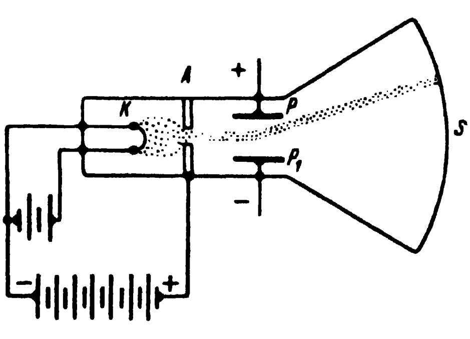

Fig. 207. Diagram of cathode ray oscillograph. *K*—cathode; *A*—anode; *P* and P_1—condenser plates; *S*—screen.

But the most perfect system recording without any inertia is a beam of cathode rays used in *cathode ray oscillographs* (Fig. 207). The cathode (electron) beam is obtained as follows. Two electrodes are placed in a vacuum glass tube at a certain distance from each other: one of these electrodes, having the shape of a thread, serves as the cathode, while the other, having the shape of a disc with a small aperture in the middle of it, serves as the anode. If a high direct tension (of about 1,000 volts) is brought to the electrodes, the cathode gives rise to a rectilinear stream of free electrons. Passing through the aperture in the anodal disc the cathode beam falls on a fluorescent screen formed by the bottom of the tube and produces a luminous spot there. The latter can be recorded on a photosensitive film. In order to intensify the electron stream the thread of the cathode is incandesced by means of a current passed through it from a separate small battery.

The potential to be recorded is led off to the plates of a condenser situated inside the tube on both sides of the cathode beam. Consisting of negatively charged electrons the latter passes between the plates of the condenser and always deviates in the direction of the plate which at the given moment carries a positive charge. In this way the form of any impulse of a potential, however short its duration, can be reproduced with precision.

But the loop and cathode ray oscillographs cannot be directly used for recording action currents because they are not sensitive enough. Action currents led off to an oscillograph must therefore be considerably amplified. This is done by cathode valve amplifiers whose principle of operation is described in text-books of physics.

As before stated, the action current is due to the fact that the excited section of the tissue is for a short time electronegative to the resting sections. When one of the leads is applied to the uninjured part of a nerve or muscle and the other to an injured part, the difference of potentials between the electrodes during the passage of the excitatory wave beneath the first electrode will for a short time diminish: the recording apparatus will reveal a rapid variation in the direction reverse to that of the current of rest. As to the injured section (beneath the second electrode) the excitatory wave becomes extinguished in it without changing its electric state. In this case the action current has a form of a monophasic wave (Fig. 208, *a*).

But if both electrodes are applied to the uninjured longitudinal surface of the preparation, the action current will appear as a diphasic wave (Fig. 208, *b*), since the sections of the tissue to which the electrodes connected with a galvanometer are applied are not affected by excitation simultaneously. Spreading at a certain velocity, the excitation first reaches the nearest electrode where it creates transitory electronegativity; the recording apparatus shows a wave in one direction. When the excitatory wave passes the region of the first electrode in its further propagation and reaches the section lying beneath the second electrode, a momentary reverse current arises in the external circuit and is recorded as a second wave in the opposite direction (see Fig. 1).

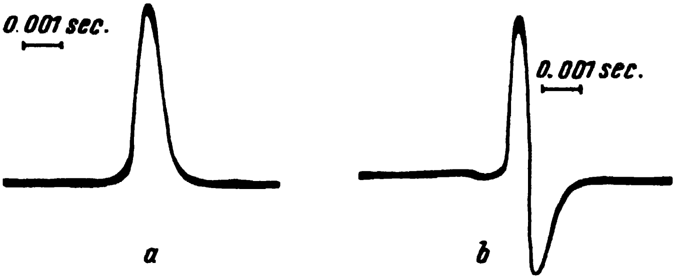

Fig. 208. Left—monophasic, right diphasic current of action in the frog's sciatic nerve recorded on cathode ray oscillograph.

In the skeletal muscles of vertebrates a monophasic action current lasts thousandths of a second: in the muscles of the frog, 0.003 to 0.004 second; in the muscles of homoiothermal animals, 0.002 to 0.003 second. In nerves it lasts 0.0005 to 0.0020 second. The more rapid the propagation of excitation along the nerve, the shorter the duration of the action current.

Correlation between electric and mechanical changes in muscle. Simultaneous recording of a muscular contraction and of the action current led off from the muscle shows that in its ascending part the action current precedes contraction. This was demonstrated by recording the action current and the curve of thickening of the frog's muscle.

This is also obvious from a simpler experiment which is a variant of the experiment with secondary contraction (page 503). If the nerve of a nerve-muscle preparation is placed on the heart of the frog so as to bring it into contact with the base and apex of the ventricle, the muscle of the preparation will contract at each systole. In this case the nerve is stimulated by an action current which precedes the contraction of the ventricle. Since the latent period of contraction of the cardiac muscle is relatively long, the contraction of the preparation each time precedes the contraction of the heart.

According to the data obtained by means of a cathode ray oscillograph, a monophasic action current of a muscle consists of two parts. The transitory ascending part of the action current which lasts about 0.003 second precedes contraction, while its slow descending part lasting from 0.05 to 0.07 second coincides with the contraction. These data testify to the fact that the transitory initial part of the action current does not represent the contractile process, but the excitatory process which precedes the contractile process in the muscle.

The difference between the electric and mechanical effects in the muscle is particularly pronounced in tetanus. When a muscle is subjected to rather frequent, direct or indirect, stimulations, the mechanical effect, as before stated (Chapter 47), is continuous; the action currents of the muscle, however, proceed separately without merging (Fig. 209). Consequently, the muscle responds to each stimulation by a very rapid and easily reversible change which is characterized by an action current and which predetermines the origination of more protracted processes underlying the mechanical effect of contraction.

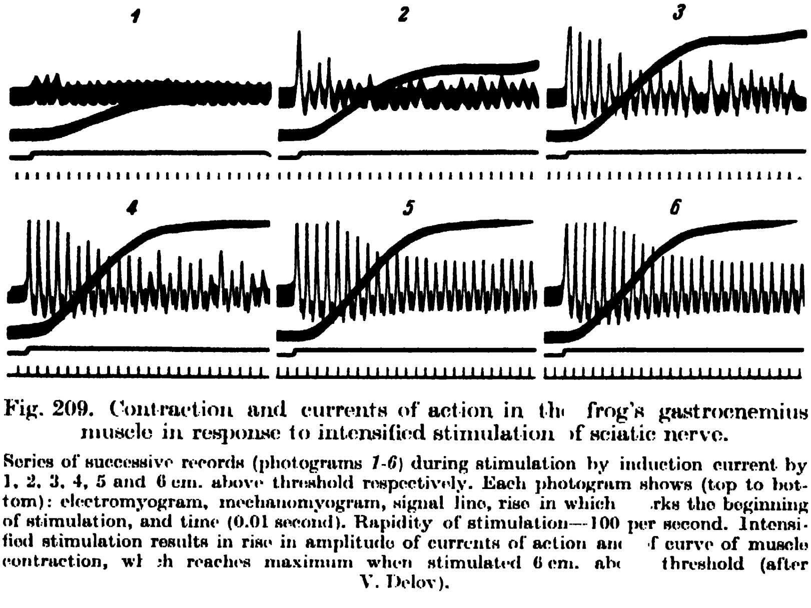

Fig. 209. Contraction and currents of action in the frog's gastrocnemius muscle in response to intensified stimulation of sciatic nerve.

Series of successive records (photograms *1-6*) during stimulation by induction current by 1, 2, 3, 4, 5 and 6 cm. above threshold respectively. Each photogram shows (top to bottom): electromyogram, mechanomyogram, signal line, rise in which marks the beginning of stimulation, and time (0.01 second). Rapidity of stimulation—100 per second. Intensified stimulation results in rise in amplitude of currents of action and of curve of muscle contraction, which reaches maximum when stimulated 6 cm. above threshold (after V. Delov).

If the stimulations are not too frequent, the number of emerging action currents may exactly correspond to the number of individual stimulations. But if the stimulations are too frequent (for example, more than 300 per second), the frequency of action currents reproduced by the muscle of the frog is reduced and, in general, becomes irregular. This intermittent character of the flow of action currents, as we shall see later (page 509), is connected with the period of inexcitability (the so-called absolute refractory phase) which arises in the tissue immediately after each excitation and which separates one excitatory wave from another.

Similarly intermittent are the action currents in human muscular contractions which are usually of a tetanic character. However transitory a human movement may be, muscular contraction is not accompanied by a single action current, but by a more or less frequent series of such currents.

Wedensky (1884) was the first to hear action currents in the human muscle with the aid of the telephone. About 30 years later similar investigations were carried out by other authors who used the string galvanometer for recording action currents. An electrogram of muscular contraction (Fig. 210) is expressed by approximately a 50-fold rhythm of the basic waves complicated by small accessory oscillations. The latter are accounted for by the fact that individual groups of muscle fibres do not contract strictly simultaneously.

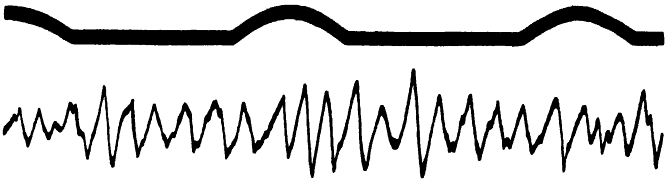

Fig. 210. Action currents of biceps during flexion of arm in elbow. Upper line marks time in fifths of a second (after Pieper).

The study of action currents led off from a very small number of human muscle fibres shows that in each fibre the frequency of the excitatory impulses may vary from 3 or 5 to 50 and 70 per second, and that it increases within these limits when the contraction is intensified (Adrian et al.). In weak muscular tension, different groups of fibres—motor units—do not contract simultaneously, and the frequency of impulses in each group is low so that individual groups may produce not a continuous but an incomplete tetanus. In the muscle as a whole, however, the contractile effects of individual fibre groups merge into a smooth contraction. Intense contractions involve more acting motor units and more frequent impulses in each of them so that various groups of muscle fibres act more synchronously.

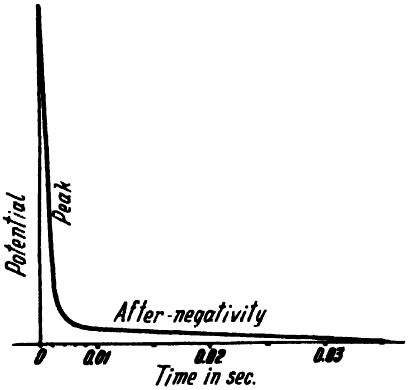

Fig. 211. Correlation between "peak" and after-negativity in fibres of the frog's sciatic nerve (after Gasser).

Electric after-potentials. The aforesaid action current appears as a transitory modification of electric potentials. In the muscle the ascending part of such an action current almost comes to an end before the development of mechanical contraction begins; in the nerve it is still shorter and lasts for about 0.001 second. But the use of amplifying devices, recently introduced in the investigation of bio-electric currents, has shown that the aforesaid action currents are only the initial, most appreciable phase of the changes in electric potentials in the excited part of the tissue. This initial, "high-voltage" part of the action current, which may be called its spike is directly succeeded by a "low-voltage" negative after-potential

(Fig. 211) lasting hundredths of a second and over (Vorontsov, Erlanger, Gasser et al.).

In a fresh-prepared nerve the value of the initial part of the negative after-potential does not exceed 0.01 of the value of the spike. It disappears in the nerve only in 0.02 to 0.03 second (Fig. 211), and in the muscle in 0.05 to 0.07 second. Treatment of the tissues by certain substances (veratrine, calcium and barium salts, etc.) intensifies the negative after-potential by scores of times and prolongs its duration to whole seconds. On the contrary, narcotics and potassium salts suppress the negative after-potential even when they are used in such small concentrations as to exert no appreciable influence on the value of the spike.

In the nerve deprived of oxygen supply there is no negative after-potential. In the nerve poisoned by veratrine it is heightened, and a certain rise in respiratory metabolism is observed. This close dependence of the negative after-potential on the chemism of the medium and on the presence of oxygen warrant its connection with the recovery processes going on in the tissue after the period of excitation. Contrary to this, a leading role in the very propagation of excitation is often ascribed to the initial part of the action current, or the spike.

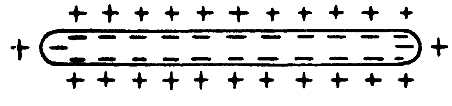
Fig. 212. Diagram of uninjured polarized nerve fibre (at rest).

The negative after-potential is succeeded by a positive aftereffect. It is usually smaller than the negative after-potential in amplitude, but considerably exceeds it in duration. The positive aftereffect becomes much more intense after rhythmic stimulations of the nerve.

There are indications (Gasser et al.) that the negative after-potential is accompanied by heightened excitability in the nerve, the positive aftereffect by a decrease in excitability.

The origin of currents of rest and of action currents. Already Sechenov pointed out the significance of metabolism for the emergence of potential differences in animal tissues. Developing this viewpoint, V. Chagovets (1896) showed that it was possible to explain the electric phenomena in the muscles and nerves by proceeding from the concepts of concentration currents determined by different concentrations of certain ions (for example, H-ions) in various sections of the tissue. The difference in concentration may result from modification of metabolic processes in the excited or injured areas.

Later, the membrane theory (Bernstein, 1902) became widespread; this theory is based on the schematic conception that on the surface of the muscle and nerve fibres there exists a special marginal layer (membrane) which, like some artificial membranes, is permeable to cations and impermeable to anions. Since the concentration of electrolytes on both sides of the membrane is not equal, the cations (for example, potassium ions which are relatively abundant inside the fibre) tend to pass into the external medium, but are retained on the outer surface of the membrane by the charges of their anions. Owing to this, the membrane becomes polarized: its outer surface is charged positively and the inner surface negatively (Fig. 212). So long as the fibre is not injured, the potential is equal along its entire surface, but when it is injured, i.e., when the integrity of the membrane is violated, the negative ions are able to diffuse from within to the exterior: the injured site proves to be electronegative to the normally polarized surface.

Such is the origin of the current of rest. As to excitation, it is connected with an increase in the permeability of the membranes which is proved by a number of observations. Owing to this, the excited section of the membrane becomes equally permeable to all ions and is depolarized, as a result of which the excited section proves to be electronegative to the remaining, positively charged surface of the fibre. Unlike depolarization resulting from an injury, depolarization caused by excitation is reversible and is propagated together with the excitatory wave. From this point of view the propagation of excitation appears as propagation of the depolarization wave. The difference of potentials on the border line between the depolarized and polarized sections gives rise to a displacement of ions which leads to the depolarization of a new section and to the repolarization of the previous section (Fig. 213).

It must be pointed out that the very existence of semipermeable membranes in the tissues is disputed (D. Nasonov); there are reasons, however, for attaching importance to the surface of division between different phases of living substance and to differences in the concentration of ions.

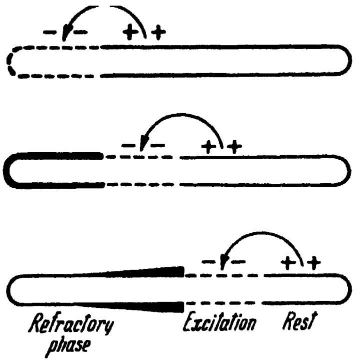

Fig. 213. Diagram showing depolarization of membrane of nerve fibre in stimulated area (this section is shown by dotted line); excitation is propagated from left to right and leaves refractory period behind (this section is shown by heavy line). Arrows show rise of local current.

The Refractory and Exaltation Phases

The study of electric phenomena in nerves and muscles leads to the conclusion that excitation is an intermittent and rhythmic process. Its intermittent character is connected with the refractory phase arising after each flash of excitation. Following an impulse of excitation, the tissue does not react for a certain, very short, period of time to even the strongest new stimulation. This period of complete inexcitability, conditioned by a preceding process of excitation, is called the *absolute refractory phase*. After this the tissue gradually recovers its excitability evident from the thresholds of stimulation which gradually drop to the initial level. This is the so-called *relative refractory phase*.

The periods of inexcitability split the process of excitation into separate flashes—impulses accompanied by an action current. Whatever the frequency with which the nerves and muscles are stimulated, the action currents never merge in them. A record of action currents during

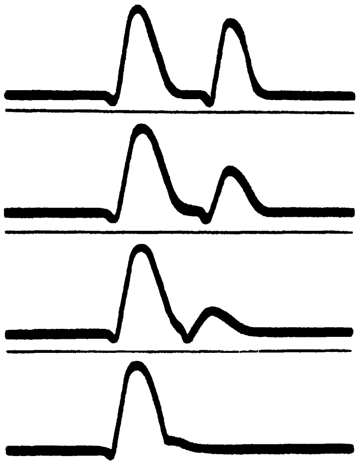

Fig. 214. Currents of action in the cat's diaphragmatic nerve with two successive stimuli.

With diminution of the interval between stimulations second current of action diminishes and, finally, disappears (bottom record), because it occurs within refractory period of the first. Lower periodic curve marks time of 0.001 second during the period (after Gasser).

two rapid successive stimulations shows that when the interval between the stimulations is shortened the action current produced by the second stimulation gradually diminishes and, finally, at a very short interval, fully disappears (Fig. 214).

The relative refractory phase expressed in lowered excitability is succeeded by a phase of heightened excitability which was discovered by Wedensky and named the *exaltation phase.*

The excitability changes in a nerve-muscle preparation after excitation may be presented graphically. Fig. 215 shows that the absolute refractory phase which characterizes the state of complete inexcitability of the preparation lasts 0.0025 second. The subsequent recovery of excitability to its initial level, i.e., the relative refractory phase, terminates 0.012 second after the onset of excitation. The state of heightened excitability observed after that, i.e., the exaltation phase, is succeeded by the normal state 0.030 second after the onset of excitation.

The exaltation phase may in some cases be prolonged to 0.1 second and over. The absolute refractory phase and especially the relative refractory phase also vary. Low temperature, modifications in the ion medium and anaesthesia considerably prolong the relative refractivity.

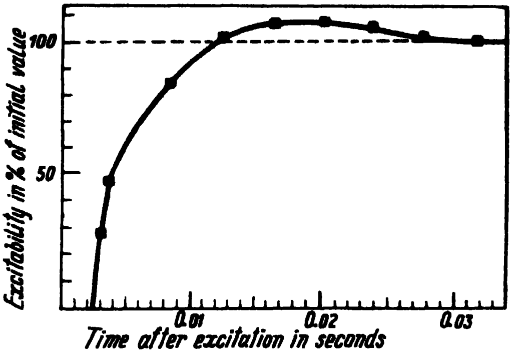

Fig. 215. Curve of recovery of excitability of nerve-muscle preparation after single stimulation of the nerve (after Adrian and Lucas).

In addition to lowered excitability of the tissue, the relative refractory phase is characterized by weaker reaction to new stimulation and by slower conduction of excitation. All these changes are the more pronounced, the shorter the interval between the stimulations, i.e., the less the tissue recovers after the preceding excitation. Contrariwise, in the exaltation phase the intensity of the reaction and the rate of conduction are higher than initially.

Recent investigations have found that after the passage of an excitatory impulse the excitability of the nerve undergoes a number of other modifications in addition to those mentioned above. For instance, a new, though less pronounced, period of lowered excitability—the *phase of subnormal excitability*—after the exaltation phase is observed (Gasser et al.). Thus excitability returns to its initial level by a series of rises and falls which are gradually extinguished.

In the muscle the refractory phase lasts longer than in the nerve. It is especially long in the cardiac muscle (page 104) and was therefore discovered there first. In homoiothermal animals the absolute refractory phase lasts only about 0.001 second in the nerve and 0.0025 to 0.0030 second in the skeletal muscle. In a mixed nerve it differs in various groups of fibres. Generally speaking, the faster the conduction in the nerve fibre, the shorter the absolute refractory period.

The following peculiar phenomenon is connected with the existence of the exaltation phase; it was first described in 1886 by Wedensky who named it a *single tetanized twitch.* If the nerve of a nerve-muscle preparation is subjected in its distal part to a subthreshold tetanizing stimulation and in its proximal part to maximal induction shocks, short tetanuses rather than simple muscular twitches are observed (Fig. 216). Electrophysiological investigations of this phenomenon substantiated Wedensky's original assumption that it was caused by a transitory rise in the excitability of the nerve

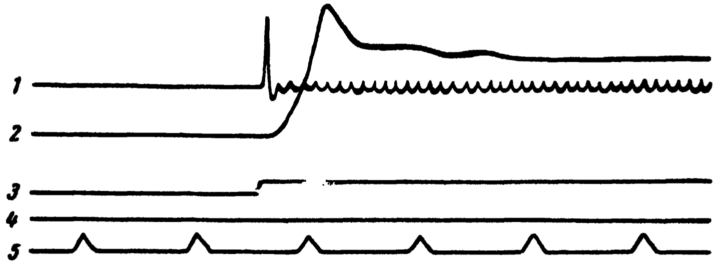

Fig. 216. Tetanized single contraction of a nerve-muscle preparation.
Proximally applied single maximal stimulus (31 cm.) is added to subthreshold tetanization of a nerve (36.5 cm. distance between coils with 36 cm. threshold). Current of action, corresponding to single stimulation, is followed by series of currents of action, equal in amplitude, reproducing frequency of subthreshold stimulation.
Top to bottom: *1*—electromyogram; *2*—mechanomyogram; *3*—record of the moment of single stimulation (rise of line); *4*—record of tetanization (recorded throughout experiment); *5*—time recorded in 0.2 second. Subthreshold tetanization with frequency of 50 per second was applied 2 seconds before single stimulus (after Vasilyev, Delov and Mogendovich).

after the passage of a single excitatory wave, owing to which subthreshold tetanization became for a short time above-threshold. This phenomenon has roused particular interest during the last decades in connection with the propositions advanced by A. Ukhtomsky who regarded it as one of the probable mechanisms of the dominant (page 575).

Dependence of Frequency of Nervous Impulses on Intensity of Stimulation

As before stated (page 507), an increase in the power of muscular contraction is normally due to an increase in the frequency of nervous impulses coming to it. This dependence is clearly seen in experiments with stimulation of a single nerve fibre which forms a motor unit together with the group of muscle fibres innervated by it. The nerve trunk in the nerve-muscle preparation is split into separate bundles and fibres, which are successively cut so as to leave only one motor fibre intact. If such a nerve is stimulated by an induction current above the site of the split, the nervous impulses will reach the muscle only along the single intact nerve fibre and act on the muscle fibres innervated by it.

By varying the strength of stimulation from a threshold to the physiological maximum without changing its frequency and simultaneously recording the mechanical contraction and the action currents of the muscle, we shall obtain the results shown in Fig. 217. Here we see that at a frequency of 100 shocks per second a weak stimulation (5 mm. above the threshold according to the scale of the induction appartus) produces only about 30 impulses per second; accordingly, the tetanic curve is not very high. A stronger stimulation (10 mm. above the threshold) produces about 50 impulses per second and a higher tetanus. Finally, with a strong stimulation

(50 mm. above the threshold) the frequency of the impulses (in this case 100 impulses per second) *strictly corresponds to the frequency of stimulation*, and the tetanic curve rises to the maximum, whereas the amplitude of the action currents, which characterizes the strength of the impulses, does not essentially change with the different intensities of stimulation.

The increased frequency of impulses under stronger stimulations is explained as follows. If a series of weak stimulations is applied, each new stimulation can create an impulse only when the excitability of the tissue, diminished by the previous impulse, is restored to its initial level. All the weak stimulations which occur at earlier moments of the refractory phase are below the threshold of excitability and produce no effect. A series of frequent but weak stimulations therefore creates a relatively low frequency of impulses. But if the intensity of stimulation is increased so that each new stimulation can excite the tissue during the relative refractory phase, impulses will arise at the same frequency at which the tissue is stimulated.

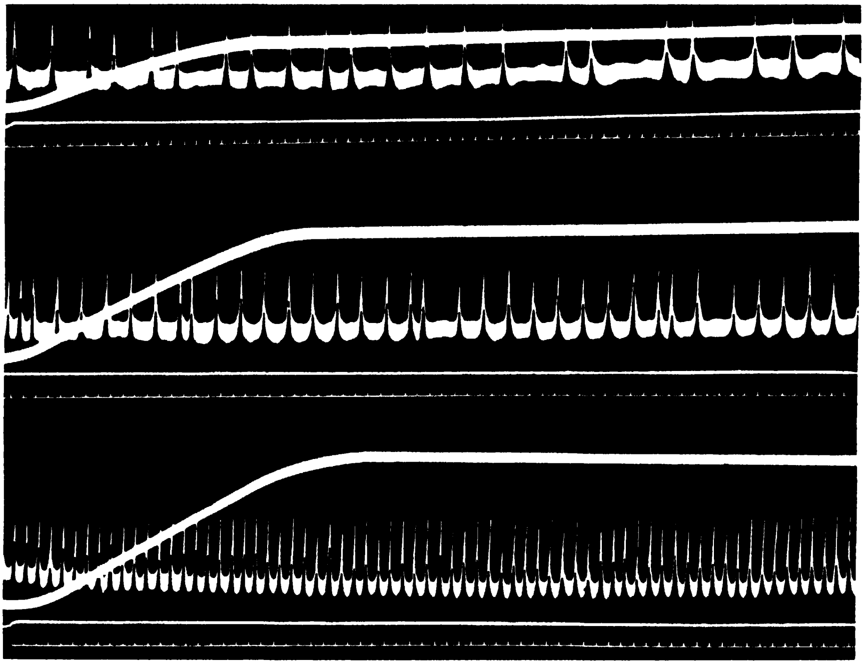

Fig. 217. Course of tetanus during stimulation of single nerve fibre by induction current 5 mm. (upper photogram), 10 mm. (middle photogram) and 50 mm. (lower photogram) above threshold. Frequency of stimulation—100 per second. Each photogram from top to bottom contains: curve of currents of action, curve of muscle contraction, signal line (its rise marks beginning of stimulation) and time recorded in hundredths of a second (after V. Delov).

Thus the gradation of muscular contractions within the limits of each motor unit is attained predominantly by an increase in the frequency of impulses. The gradation of contractions developed by the entire muscle is additionally conditioned by the different number of the acting motor units.

When not rhythmic but single stimulations are applied to the nerve fibre the height of muscular contraction remains invariable at the different intensities of stimulation if the latter is above-threshold. The same has already been stated with regard to the cardiac muscle which reacts to above-threshold stimulations of different strength with contractions of the same intensity, or does not react at all if the stimulation is subthreshold.

These facts gave rise to the formulation of the so-called "all or none" law according to which an excitable tissue produces a maximum response at any strength of above-threshold stimulation, or does not react at all if the stimulus is below the threshold.

At the same time a number of authors (Wundt, Verworn and others) tended to regard the aforesaid particular law as a universal law which governs the functioning of excitable tissues, as a principle similar to Müller's law of specific energy of the sense organs (page 671).

Experimental data, including the data obtained by Soviet physiologists, show that a relative independence of the effect on the strength of the stimulation can be attributed only to an impulse which is propagated in a single nerve fibre during a single stimulation of the latter. However, here, too, a subthreshold stimulation creates a local nonpropagated modification of the potential; consequently, one cannot say that the stimulation produces here no effect whatever. Besides, the level of "all" does not remain invariable, but changes together with the change in the functional state of the nerve fibre. Thus the very formulation "all or none" does not correspond to the facts.

Moreover, it has been quite clearly established, particularly by the researches of I. Kan and A. Ukhtomsky, that in the nerve fibres of invertebrates there is a graded dependence of the strength of an impulse on the intensity of stimulation. A similar graded dependence is observed in the region of stimulation between the intensity of direct stimulation and the power of contraction of the muscle fibres in invertebrates. Consequently, the relative independence of the strength of a nervous impulse on the intensity of the stimulation by which it is produced results from the development in the course of evolution of a special mechanism characteristic mainly of the myelinated nerves of vertebrates.

Normally all stimuli acting on the external and internal receptors of the organism produce not one, but a series of nervous impulses. By bringing a larger number of nervous elements into play a stronger stimulation also creates a greater frequency of impulses, although the strength of the impulses may within certain limits remain on the same level.

The Theory of Parabiosis

Because of the refractory phase which follows each impulse of excitation, excitable tissue can produce only a limited number of impulses per unit of time. If the absolute refractory phase lasts, for example, 0.002 second, the tissue cannot produce more than 1 : 0.002 = 500 impulses per second; at a higher frequency individual stimulations will act upon the tissue which is still in a state of complete inexcitability, owing to which the frequency of the impulses will be lower than that of the stimulation. Proceeding from this Wedensky, as before stated, introduced in physiology the concept of functional *lability* characterizing the latter by the maximal number of impulses the tissue is able to produce per second in strict conformity with the rhythm of the stimulations acting upon the tissue. For the nerves of poikilothermal animals this number is close to 500, while in homoiothermal animals it reaches 1,000; for the skeletal muscle subjected to direct stimulation it is much smaller; it is still smaller for the endings of the motor nerve in the muscle, as testified to by experiments in which the muscle is stimulated indirectly.

N. Wedensky

In studying the passage of impulses through a section of the nerve modified by the action of narcotics, salt solutions, strong electric current, heating, mechanical pressure, etc., Wedensky showed that the lability of this modified section decreased. The conduction of impulses through the modified section of the nerve situated between the site of stimulation and the muscle reveals characteristic features. The difference between the action of weak and strong rhythmic stimulations disappears first; this is the so-called *equalization stage*. As a result of further, more profound changes in this section of the nerve, a strong stimulation either evokes no appreciable muscular contraction at all, or causes only a weak initial contraction, while a weak stimulation continues to produce considerable tetanuses. This is the so-called *paradoxical stage* (Fig. 218). Finally, the modified section of the nerve loses its ability to react not only to strong stimulations, but to weak stimulations as well. Thus there arises complete inconductivity, or the *inhibitory stage*.

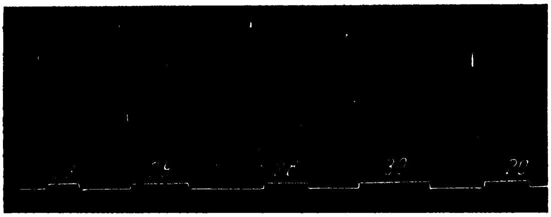

Fig. 218. Paradoxical stage.

Frog's nerve-muscle preparation during developing parabiosis 43 minutes after smearing section of nerve with cocaine. Strong stimuli (23 and 20 (distances between coils) produce rapidly passing contractions while weak stimuli (28, 29 and 30 cm.) continue to cause prolonged tetanic contractions (after N. Wedensky).

In view of these facts the theory advanced by Wedensky to explain the nature of inhibition acquires considerable importance. He believed that any agent acting on the nerve as a stimulus created by its protracted and uninterrupted action a local focus of stable and nonfluctuating excitation confined to the site of its emergence. This deepened excitation which is no longer able to spread Wedensky named *parabiosis*. When this state is fully developed the tissue seems to have lost its functional properties—excitability and conductivity—since being itself strongly excited it becomes refractory to new stimulations.

Another specific feature of parabiotic excitation, in addition to its stability and continuity, is its ability to deepen under the influence of incoming impulses of excitation. Therefore, the stronger and more frequent the incoming impulses, the stronger the local excitation in the parabiotic area and the more impeded the further conduction. The parabiotic area, characterized by extremely low lability, becomes unable to reproduce strong and frequent excitations. This accounts both for the equalization and paradoxical stages.

According to Wedensky, this also underlies the foregoing (page 467) phenomena of pessimum in a nerve-muscle preparation caused by strong or frequent stimulations (Fig. 219). In this case, however, it is the endings of the motor nerve in the muscle which form the area of lowered lability. Here the suppression of the contractile effect is not due to the fatigue of the endings of the motor nerve in the muscle, because contraction immediately recovers when stimulation becomes weaker or less frequent.

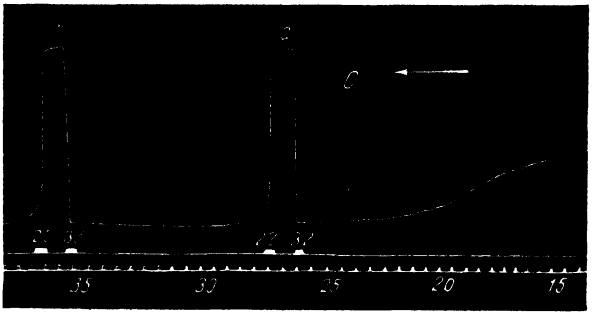

Fig. 219. Optimum and pessimum of stimulation.

uscle is stimulated from nerve (read right to left). When tetanus
rops considerably (*C*) under the action of prolonged and strong
imulus (with 22 cm. distance between induction coils) decreasing
ie stimulation (in *a*) by rapidly moving secondary coil to dis-
ance of 32 cm. from primary coil immediately enhance tetanus;
rengthening of stimulation (return to the 22 cm. distance between
ie coils) results in new relaxation of muscle. Same is repeated
ice more (*b*). Lower line marks time in seconds; line above records moments stimuli are changed (after N. Wedensky).

PART XIII

ACTIVITY OF THE NERVOUS SYSTEM

A. GENERAL CHARACTERISTICS OF THE CENTRAL NERVOUS SYSTEM AND THEORY OF REFLEXES

The physiology of the central nervous system is a particularly important link and a pivotal branch of physiological science. It reflects to a certain extent the material of all the branches of physiology, since the central nervous system influences *all* the functions of the body.

The central nervous system integrates all the processes in the organism, determines the behaviour of human beings and animals in their environment and their interrelation with surrounding nature. Developing in the course of this interrelation more than any other system of organs in the animal body, the central nervous system plays a leading part in the evolution of all the functions of the organism. In its study of the activity of the human cerebral cortex physiology comes in contact with the most essential problems of philosophy relating to human thought and consciousness. Owing to this, research into the activity of the higher part of the brain gives rise to a bitter struggle between consistent and advanced materialism (given embodiment in physiology in the great work of Pavlov) and various idealistic trends.

The "true physiology of the cerebral hemispheres" developed by Pavlov at the same time provides a basis for the study of the normal course of all physiological processes, essential not only to physiology, but also to various branches of practical medicine, hygiene, pedagogics and natural science as a whole. For a better understanding of Pavlov's reflex theory, and for better orientation in the concrete material relating to the activity of the nervous centres, it is first necessary briefly to consider the development of the reflex theory from Descartes to Pavlov.

CHAPTER 51

DEVELOPMENT OF THE PHYSIOLOGY OF THE CENTRAL NERVOUS SYSTEM. PRE-PAVLOVIAN AND PAVLOVIAN THEORIES OF REFLEXES

Development of Research into the Activity of the Brain

In 1932 I. Pavlov wrote: "Although Leucippus of Miletus proclaimed that there was no effect without cause and that everything arose from necessity, is it not still believed, even leaving man aside, that there are spontaneously acting forces in the animal organism? As for man, do we not still hear talk about free will and is there not a conviction rooted in many minds that there is something in us which is not subject to determination?... What is meant, of course, is not the temporary difficulties of research, immense as they are, but the impossibility in principle of complete determination.... This conviction also persists among some psychologists, although masked by references to the *peculiar nature of mental phenomena,* behind which, despite seemingly scientific arguments, can be detected the dualism and animism that is still immediately shared by many thinking people...."*

For a long time science was in possession only of observations showing that lesions of the brain were followed by changes in the mental activity. Such facts as the loss of consciousness as a result of a blow on the head, or a psychical change after an injury to the brain, enabled already Erasistratus (3rd century B. C.) to assert that the brain was an organ of thought. All materialistically-minded physicians, biologists and philosophers concurred in this thesis (which was also accepted by some idealists with the reservation, however, that the activity of the brain was "governed" by a nonmaterial soul).

Physiologists who beginning with Flourens (in the twenties of the 19th century) extirpated the cerebral hemispheres first in birds and later in dogs, found that after this operation the animals could no longer orient themselves in the environment, did not take food without assistance, did not avoid obstacles in their way and lost all the habits acquired prior to the extirpation of the brain (for example, they did not even recognize their master). Numerous investigations carried out somewhat later showed that the removal of different parts of the brain variously impaired the animal's movements and its reactions to the stimulation of receptors.

These experiments, the experiments with electrical stimulation of different areas of the cerebral cortex, and a number of clinical observations, gave rise to the theory of localization of functions in the cerebral cortex (Chapter 64), which only half a century ago made up the entire available material concerning the experimental study of the higher division of the central nervous system. Facts of essential importance were accumulated and as a result of their consideration from a purely metaphysical point of view, characteristic of analytical physiology, the central nervous system was often pictured as an aggregate of centres, each of which possessed invariable properties and controlled a very definite function. The criticism of this metaphysical viewpoint, unable to explain the changing activity, properties and significance of the central nervous system in the course of evolutionary and individual development, came down to a negation of the special features in the functions of the different structures of the cortex. This conception of equipotentiality of various parts of the brain divorced the functions of the brain from their material substratum and admitted operation of nonmaterial factors.

It should be added that prior to Pavlov all the facts accumulated by physiologists and relating to the activity of the cerebral hemispheres, this, according to Pavlov, "most extraordinary of all apparatuses" were interpreted in terms and concepts of psychology—a science based on a subjective evaluation by man of various mental states determined by processes which develop in the higher divisions of the brain.

Origin of Concepts of the Reflex and Their Development Prior to Sechenov and Pavlov

In Latin *reflex* means reflection,** a term which in physics designates the phenomenon of rays of light being thrown back by a reflecting surface.

The term "reflection" was first used by René Descartes, French thinker, mathematician and naturalist (1595-1650), to describe the reactions of the organism to stimulation of the sense organs (until the end of the last century the external receptors were designated exclusively by the term "sense organs"). On the basis of winking invariably produced by stimulation of the cornea, Descartes advanced the idea that the nervous excitation coming to the brain from the sense organs was reflected by the brain to the nerves controlling the muscles. He believed that all movements of animals were subject to the law of reflection by the brain of "animal spirits"—minutest particles transmitted by the nerves from the sense organs to the brain and directed by the latter through fine "pores" to the nerves extending to the muscles.

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* I. Pavlov, *Complete Works,* Vol. III, Book 2, pp. 164-65.

** In his works Sechenov not infrequently used the terms "reflected movements" and "reflective activity" as synonymous with the terms "reflex movements" and "reflex activity."

By regarding reflexes as never-changing acts, Descartes believed their nature to be determined by the structure of the nervous system. At the same time he *opposed* reflexes to the phenomena of consciousness, i.e., to the highest manifestations of the activity of the human brain. Subsequently, the entire experimental development of the reflex theory, until it was reshaped by Pavlov, was confined, in the main, to the concretization and elaboration of these propositions, characteristic of the mechanistic trend in natural science.

After Descartes, the concept of reflected actions, i.e., that of reflexes, was developed by the outstanding Czech naturalist G. Procházka in the last third of the 18th century. By that time various motor acts of decapitated (decerebrate) frogs had been described. It was observed that these movements invariably arose in response to stimulation of definite areas of the skin and that the *destruction of the spinal cord* (experiment of R. Whytt, 1764) *resulted in their disappearance*. The idea of reflex, however, has become fundamental in the physiology of the nervous system only since the thirties of last century when the English physician Marshall Hall and the German physiologist Johannes Müller, following Descartes and Procházka, began to apply the term "reflex" to "involuntary" acts that could be performed in the absence of the higher divisions of the brain and whose nature (in their judgement) was determined *only* by the kind of receptors subjected to stimulation.

At present by reflexes we imply *all* reactions of the organism produced by stimulation of receptors and effected with the participation of the nervous system (in the higher mammals normally involving the cerebral cortex). Although prior to Pavlov reflexes were also defined as reactions to stimulation of receptors (this much remained invariable), most 19th century scientists (except Sechenov) regarded them as reactions depending *exclusively* on the activity of the lower divisions of the central nervous system—spinal cord and medulla oblongata or the brain stem. Instead of a generalizing conception interpreting all forms of behaviour as reflex activity, physiology prior to Pavlov implied by reflexes only those reactions which were produced with invariable exactitude by stimulation of receptors and characterized the behaviour of animals deprived of the higher divisions of the central nervous system.

The invariable reactions by decerebrate animals to each stimulation of the receptors was the corner-stone of the entire reflex theory prior to Pavlov. This fact in itself is correct, since certain reflexes are always reproduced in the same way only after the removal of the higher nervous centres. For example, the cat with extirpated cerebral hemispheres, whatever the position in which it is placed, will always recover an upright position, thus exhibiting the "righting reflex" (Chapter 59). But it is a well-known fact that the normal cat can assume various postures. Stimulation of the cornea always provokes winking, but a normal animal may also react otherwise to this stimulation (for example, by moving off, biting, etc.), which prior to Pavlov was regarded as voluntary reactions, i.e., not determined. Hence the conclusion that two categories of phenomena existed in the human and animal organism: on the one hand, invariable reflexes depending solely on the activity of the spinal cord, medulla oblongata, or brain stem and predetermined by the nature of the stimulation of receptors by which these reflexes were produced; on the other hand, "voluntary" actions which were not determined by the stimulations which produced them, but were conditioned by the activity of the higher divisions of the central nervous system. The first phenomena were interpreted as resulting from the operation of a mechanism whose properties were determined by its structure, i.e., chiefly by the disposition of the neurons included in the reflex arc, while the "voluntary" actions were regarded as a manifestation of mental activity.

Although many researchers believed that mental activity resulted from the work of the brain, they considered this activity inaccessible to investigation by physiological methods. Therefore, as stated by Pavlov, "...for the first time since the days of Galilei the irresistible march of natural science has been held up quite perceptibly before the study of the higher divisions of the brain, the organ of the highly complex relationship between the animal and the external world. And it would seem that this is not fortuitous, that this is indeed a critical moment in natural science, since the brain, which in its higher form—the human brain—created and is continuing to create natural science, itself becomes the object of this science."*

The difficult transition from the study of spinal medullar or midbrain reflexes to the knowledge of the integral activity of the nervous system could be successfully accomplished by virtue of the work of the great naturalists Sechenov and Pavlov.

Reshaping of the Reflex Theory by Sechenov and Pavlov

Sechenov's work of 1863 was the first attempt to extend physiological analysis to the most complex phenomena of nature, the phenomena of consciousness. In this work originally entitled *An Attempt to Introduce Physiological Principles into Mental Processes* (upon the insistence of the tsarist censorship it was given the title *Reflexes of the Brain*) Sechenov asserted that the most complex phenomena of mental activity were basically *reflex* acts. Sechenov interpreted the reflexes not as strictly limited reactions in each case involving only a definite effector organ, but *as integral acts of the organism's behaviour.* He regarded the reflexes as the most general mechanism of nervous reactions which ensured the connections of the organism with the external environment and acquired special qualitative features as a result of the activity of the brain.

Sechenov's book was a synthesis of the progressive ideas of the philosophy of natural science in the sixties of last century; it considerably surpassed the level of experimental physiology of the time. When Sechenov published his book there were no methods for investigating the physiological processes developing in the brain of a *normal* animal. The idea of reflex could therefore be applied to the analysis of the work of the brain only in the "brilliant flight" of the theoretical thought of a genius (as Pavlov appraised Sechenov's book), rather than under concrete laboratory conditions. But Sechenov's book was a bold and impassioned plea to extend natural-scientific analysis to all phenomena of life, including the most complex forms of interaction between the organism and the external environment established by the activity of the brain. This plea was translated into reality by Pavlov.

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* I. Pavlov, *Complete Works*, Vol. III, Book 1, p. 113.

The transition of physiology from the study of the processes considered purely physiological to those referred to as psychic (even in animals), began for Pavlov with the question as to the way he should investigate the phenomenon of the so-called psychic excitation of the salivary glands (i.e., of salivation at the sight of food or as a result of teasing by food, etc.).

One of Pavlov's associates attempted to explain this excitation "... from a subjective point of view, i.e., proceeding, by analogy with ourselves, from an imaginary inner world of dogs ... from their thoughts, feelings and desires." As stated further by Pavlov, he and his associate "... fully disagreed on the interpretation of this world, and no further attempts on our part could bring us to any common conclusion."* The associate "... persisted in the subjective interpretation of phenomena ..." while Pavlov "... surprised at the fantastic character and scientific futility of such an attitude towards the task to be solved ... after a difficult mental struggle ... decided ... to remain even in respect of the so-called psychic excitation in the role of a pure physiologist, i.e., of an objective observer and experimenter who deals exclusively with external phenomena and their interrelations."** Having taken to this way, Pavlov interpreted the "psychic excitation" of the salivary glands as *qualitatively peculiar reflexes*. He disclosed the laws which govern the formation of countless new reflex acts elaborated during the lifetime of each individual and determining the entire activity of higher organisms; by his theory of conditioned reflexes he ushered in a new era in the development of biological and medical science.***

Pavlov's transition to the study of "pure physiology of the brain" was conditioned by his desire to know the *normal* activity of the organism as a whole, which was characteristic of his entire scientific work. In his researches devoted to blood circulation and digestion, Pavlov still divorced psychic processes from reflexes, and, according to his own subsequent statement, judged very "freely and easily" of the emotions of the experimental animals. But even at that time Pavlov was *the only physiologist engaged in the study of normal reflex acts.*

At the time none but Pavlov had any methods for studying the work of the internal organs in normal animals (and no one strove for it even with a fraction of the consistency and persistence which were so characteristic of Pavlov). Pavlov investigated all the processes of digestion and the mechanism responsible for the constancy of blood pressure, aiming, in the final analysis, to learn about the normal work of the organs of digestion and blood circulation under conditions of the organism's natural relations with the environment. Whereas prior to Pavlov physiologists studied reflexes mainly by experimenting on animals deprived of the cerebral hemispheres, Pavlov investigated the normal reflex acts of integral organisms. Only these reflexes of the organism could be regarded as fundamental factors of its adaptation to the external environment. Thus, the entire system of Pavlov's previous researches, aimed at studying the normal functions of the organism as a whole, paved the way for a transition to the study of conditioned reflexes.

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* *Ibid.*, p. 13.

** *Ibid.*, p. 14.

*** Pavlov first reported on his new ways of research at the International Medical Congress in Madrid, in April 1903. The study of conditioned reflexes was begun in 1901 in Pavlov's laboratory by I. Tolochinov.

Pavlov's theory of conditioned reflexes "... led to the creation of a new branch in the physiology of animals—the physiology of the higher nervous activity, as the first chapter in the physiology of the higher division of the central nervous system."* Only with the development of this theory could natural science begin to solve "... the persistent, fundamental question: what is the connection between the brain and the animal's or our own higher activity?"**

I. Pavlov

The elaboration of the theory of conditioned reflexes began with the natural-scientific analysis of such a seemingly simple and—compared with the whole organism—minor phenomenon as the secretion of saliva under the action of agents usually preceding the process of eating. The expression "the mouth waters" existing in many languages shows that the above fact itself was known long ago. Only the genius of Pavlov, however, was able to discern in this fact "... an elementary mental phenomenon which at the same time could be fully and rightly regarded as a purely physiological phenomenon; beginning with it—with a strictly objective study (as is generally done in physiology) of the conditions of its emergence, its various complexities and its disappearance—one could obtain first of all an objective physiological picture of the entire higher nervous activity of animals, i.e., the normal functioning of the higher part of the brain, instead of *the* previous experiments involving *its* artificial stimulation and destruction."*

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* I. Pavlov, *Complete Works*, Vol. III, Book 2, p. 320.
** *Ibid.*

Fundamental Principles of Pavlov's Reflex Theory

Pavlov wrote: "The theory of reflex activity is based on three fundamental principles of exact scientific investigation: firstly, the principle of determinism, i.e., an impulse, impetus or cause for every given action or effect; secondly, the principle of analysis and synthesis, i.e., the initial break-up of the whole into its parts or units, and the subsequent gradual re-establishment of the whole from these units and elements; and, finally, the principle of structure, i.e., the disposition of the activity of force in space, the adjustment of dynamics to structure."**

The principle of determinism, as before stated, lies in the consistent application of the law of material causality to all phenomena *without any exception* and in all organisms. This means that all natural phenomena, including the most complex, are always determined by the causes which evoke them, and that in the presence of such causes the phenomenon which is called forth by them must inevitably occur. This conception of determination of all phenomena in the organism advances the propositions of Sechenov who stated that "... all acts of conscious and unconscious life are reflexes by their origin."***

This principle of determinism rejects the conception of "voluntary" actions, as actions arising spontaneously, i.e., without any external cause. And it was not without reason that in referring to the spontaneous emergence of bio-electric currents in the medulla oblongata, Sechenov specified that the term "spontaneous" did not disclose the nature of the phenomenon produced by an undoubtedly existing though still unknown cause. Although science is still unable to explain the origin of a number of phenomena in the organism and although with the progress of science more and more natural phenomena, that are still obscure, will be elucidated, materialistic natural science is based on the thesis that every occurrence in the world has its material cause. It is precisely on the basis of this fundamental proposition that Pavlov developed his theory of conditioned reflexes.

The principle of analysis and synthesis, as applied to the investigation of the brain, consists in the fact that by its activity the central nervous system, mainly its higher division, constantly dismembers, breaks up the stimuli acting on the receptor mechanisms, and at the same time synthesizes, unites into various complexes the action of stimuli separated in the course of analysis (Chapter 62).

The principle of structure in the reflex theory signifies that any nervous process develops in definite morphological structures. The specific features of various reflexes always depend on the processes going on in the different structures of the central nervous system. Function and structure determine each other. We still know very little of the delicate changes taking place in the various nervous structures and in the interconnection of different groups of nerve cells in the course of reflex activity. Many questions arise here at every step. But we do know that there is not a single phenomenon in the most complex forms of the higher nervous activity which is not determined by material processes going on in numerous formations of the brain whose structures and functions are diverse and changeable.

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* *Ibid.,* p. 322.

** *Ibid.,* p. 164.

*** I. Sechenov, *Selected Works,* U.S.S.R. Academy of Sciences, 1952, p. 124.

CHAPTER 52

GENERAL CHARACTERISTICS OF REFLEX ACTIVITY

Pavlov pointed out that the nervous system was the most complex and delicate instrument on our planet; that by means of this system connections were established between the numerous parts of the organism and between the organism, as a highly complex system, and the innumerable external influences. These connections are established through reflexes.

Reflexes

All acts of the organism in response to stimulation of the receptors and involving the central nervous system are reflexes.

Giving a general description of reflex activity Pavlov wrote: "...A certain agent of the external world or of the organism's internal environment produces a certain effect in one or other nervous receptors; this effect is transformed into a nervous process, into nervous excitation. The excitation is transmitted along certain nerve fibres, as though along an electric cable, to the central nervous system; thence, thanks to the established nervous connections, it passes along other nerve fibres to the working organ, where it is transformed into a special activity of the cells of this organ. Thus, the stimulating agent is indispensably connected with the definite activity of the organism, as cause and effect."*

Normally reflexes are produced only by stimulation of receptors. Artificially they can be produced by stimulation of the afferent nerves which extend from the receptors; this can be illustrated, for example, by the secretion of saliva in response to stimulation of the afferent fibres of the lingual nerve (page 244). This method is often used in experiments connected with the study of reflex activity. Direct stimulation of afferent nerves is sometimes also observed in man in pathological cases, for example, when the nerve trunks are compressed by tumours. Such stimulation may give rise to abnormal reflexes: for example, prolonged hiccup during stimulation of the afferent fibres of the phrenic nerve, vomiting during stimulation of certain sensory fibres of the vagus, etc.

Reflexes may be divided into two categories: unconditioned and conditioned reflexes. Normally each reflex act is almost invariably a complex of unconditioned and conditioned reflexes united in integral complex reflex acts. These two categories of reflexes, however, differ in *the mechanism of their origin.*

Unconditioned reflexes are inborn reactions of the organism; they are similar in all individuals of the same species and manifest themselves in effects whose nature is determined in typical cases only by the receptors stimulated and the strength of this stimulation. Each unconditioned reflex therefore has its *receptive field*; the latter covers the area containing all the receptors, whose stimulation causes the given reflex (Fig. 246). Unconditioned reflexes can be effected, though in a somewhat modified form, after the removal of the cerebral hemispheres. These are the reflexes which were investigated long ago; prior to Pavlov, however, they were studied apart from the normal activity of the integral organism.

Conditioned reflexes are formed in the course of the organism's individual life; in higher animals they necessarily involve the cerebral cortex.

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* I. Pavlov, *Complete Works*, Vol. IV, p. 22.

Their elaboration is due to the formation of temporary connections, while the effect of each conditioned reflex depends not on the nature of the stimulation which produces it, but on the kind of the other nervous act with which this stimulation coincided in time.*

Evolution of the Structure and Functions of the Nervous System

At the earliest stage of development of the nervous system in the phylum Coelenterata (for example, the medusa), special receptor structures appear on the surface of the body in the shape of modified epithelial cells. Their endings, turned inside the body, come in contact with a network of fibres of the nerve cells; this network is underlain by muscle cells which function as effectors. Thus, already *at the very early stages of its phylogenetic development the nervous system ensures connections between the receptors and effectors.*

In the course of evolution both the receptors and the nerve cells undergo differentiation. Receptors for *light, sound and smell stimulations* (the so-called distant receptors) develop in the anterior part of the body. Already in worms the main mass of nerve cells collects in large aggregates forming the central nervous system. In all invertebrates the latter is represented by ganglia; in the vertebrates, by the spinal cord and brain.

In all animals the central nervous system is a region where connections between the afferent nerve fibres, extending from the receptors and the nerve cells giving off axons to the effectors, are established.

As the central nervous system evolves, the connections between the receptors and effectors grow more and more complex. An ever-increasing number of internuncial neurons appear between the afferent and efferent neurons. Masses of nerve cells develop and are superimposed, as it were, on the phylogenetically earlier structures of the central nervous system. In the invertebrates it is the ganglia lying in the anterior part of the body which develop most, while in the vertebrates it is the brain (see Fig. 262), in the brain the cerebral hemispheres, and in the latter—the cortex.

As the relations between the organisms and the environment grow increasingly complex, the functions and structure of the central nervous system become likewise modified and more complex. The conditioned reflexes elaborated during the lifetime become more important than the inborn, unconditioned reflexes (instincts). The function of the nervous system incessantly changes and grows more complicated, beginning with the Coelenterata, which react only to a limited number of stimuli applied directly to their bodies, and all the way to man whose activity is determined by social factors and leads to his knowledge of the surrounding world and the ability to transform it. But in all cases the activity of the nervous system is of a reflex nature; in all animals this activity forms, according to Pavlov, the basis "... of that infinite adaptability in all of its manifestations which constitutes life on earth."** To this Pavlov added (1903): "Are not the movements of plants towards light and the seeking of truth through mathematical analysis essentially phenomena of the same order? Are they not the last links of an almost endless chain of adaptation taking place throughout the living world?"*

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* An elementary description of conditioned reflexes was given in Chapter 3; several examples illustrating the nature of conditioned reflexes were cited by us when considering various functions of the organism; a special study of these reflexes is made in chapters 60-65.

** I. Pavlov, *Complete Works,* Vol. III, Book 1, p. 38.

Concepts of the Reflex Arc and the Nervous Centre

Each reflex is produced by the activity of certain structures of the nervous system. A combination of structures involved in the accomplishment of each reflex is called a *reflex arc.*

From the definition of reflexes it is clear that each reflex arc must necessarily include the following links (see Fig. 3):

a receptor apparatus	→	a nervous centre	→	an effector
(including receptors and afferent nerve fibres which connect them with the central nervous system)		(groups of neurons of the central nervous system)		(including various organs of the body with the efferent nerve fibres which innervate them)

In a more detailed form the same links should be represented as follows:

receptor → afferent fibre → nervous centre → efferent fibre → effector

When reflexes were interpreted as constant reactions of the organism, whose nature depended on the kind of receptors and stimuli by which they were produced, each reflex was considered to possess its own, inborn reflex arc. The discovery of conditioned reflexes showed that reflex arcs were formed not only in the process of the phylogenetic development of the central nervous system, but also in the course of its functioning.

The nerve structures entering the central part of the reflex arc are called the centre of the given reflex. Normally the reflex responses of the organism to the stimulation of receptors are complex reflex acts which include unconditioned and conditioned reflexes united into an integral whole. It follows that the centre of each complex reflex is a combination of several groups of neurons situated at different levels of the central nervous system.

The entire activity of the central nervous system is of a reflex nature. The nervous structures described as centres of various functions (respiration, vasomotor action, vomiting, thermoregulation, urination, erection, pilomotor activity, etc.) are therefore reflex centres. The latter, as before stated, cannot have any localization adjusted to one definite point of the central nervous system. In his statements concerning the food centre, Pavlov emphasized that it was situated at various levels of the central nervous system.

This is also true for the centres of all activities of the organism. Each of these activities depends on the action of certain agents which evoke unconditioned and conditioned reflexes united into complex reflex acts that govern the given activity (for example, respiration, thermoregulation, circulatory regulation, etc.).

The centre of each function, consequently, takes in all the nerve structures at different levels of the central nervous system (including the cerebral cortex) involved in the accomplishment of reflex acts which ensure the performance of the particular function. As Pavlov stated "...the main centre of gravity of the nervous activity lies precisely in the receptive part of the central relay station; herein lies the source of progress of the central nervous system accomplished by the brain, by the cerebral hemispheres; here is situated the principal organ responsible for the most perfect equilibration with the external world, which is embodied in the higher animal organism."*

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* *Ibid.*

The neuron theory. The nervous system consists of a multitude of nerve cells (in man there are more than 15,000 million such cells). *Each nerve cell with all of its processes (axon and dendrites) is called a neuron.* The investigations carried out by a number of histologists and neurologists, such as M. Landovsky, A. Arnstein, A. Mislavsky, D. Zavarzin, B. Lavrentyev, and others (in our country), His, Held and especially Ramón y Cajal (in Western Europe), established the fact that each neuron is *to a certain degree* an independent structure. The relative independence of each neuron finds its morphological expression in the fact that the endings of the axons and dendrites of each nerve cell do not penetrate into any other cell body or into any of its processes. The endings of the axon branches of each nerve cell only come in contact with the cell bodies or dendrites of other nerve cells, forming thickenings, or knobs, on their surface (Fig. 220). The area of contact between neurons is called the *synapse*. The synapse can also be defined as the anatomical border between two neurons, since the transmission of excitation from one neuron to another through the synapse possesses a number of specific features (Chapter 53).

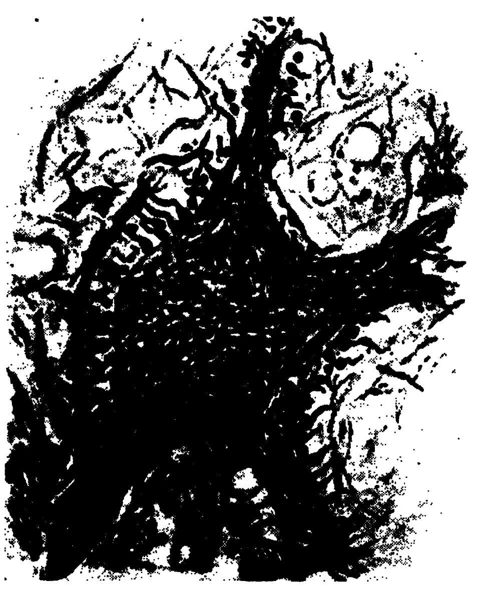

Fig. 220. Synaptic knobs (shown darker) on body and dendrites of motor cell of anterior horns of spinal cord (after K. Lavrov).

The term "synapse" is used to denote the region where the endings of the axon come in contact with nerve cells or any other cells; this term, consequently, applies not only to the interneuron junction, but also to any point of junction between the axons of efferent neurons and the cells of various effectors. In accordance with this, the points of junction between the motor nerve fibres and the muscle cells are designated as myoneural synapses, and the area of contact between the secretory nerves and the glandular cells—as neuroepithelial synapses.

The axon of each neuron in the central nervous system is in synaptic junction not with one, but with many neurons. Histological preparations of the brain (Fig. 220) show that a cell body and the dendrites of each neuron are covered on all sides by endings of axons of other neurons.

The relative independence of each neuron is functionally reflected in the fact that the transmission of excitation from one neuron to another differs from the propagation of excitation within one neuron in a number of specific features. This fact is of very great significance. The diverse reactions of the central nervous system would be unthinkable if the excitation spread over the entire brain just as it spreads within a single neuron when the excitation arising in one part of the neuron consecutively embraces the whole neuron.

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* *Ibid.*, p. 156.

The independence of each neuron is only relative, however. As Lavrentyev pointed out, "the nerve tissue is simultaneously dismembered and

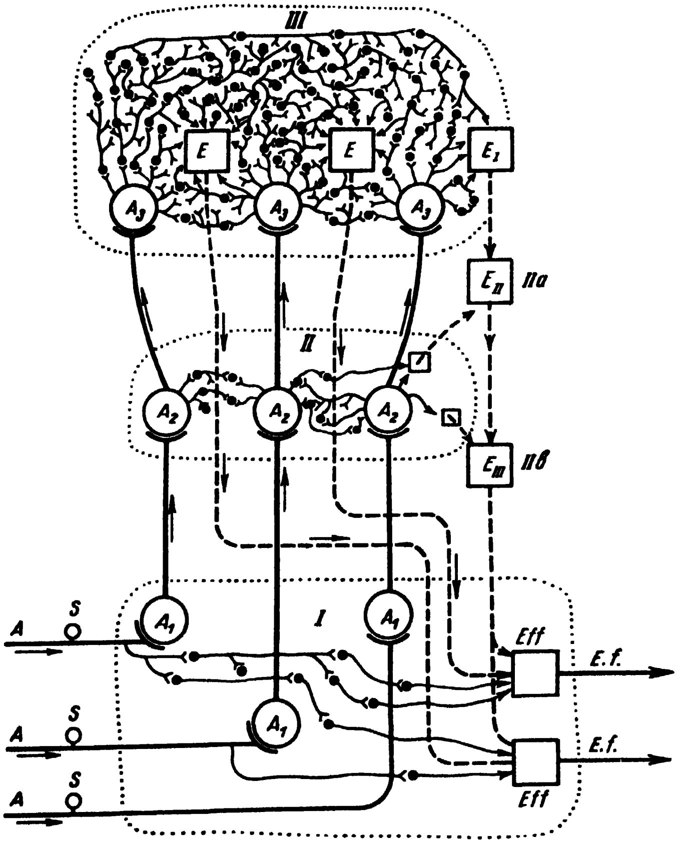

Fig. 221. Highly schematic diagram of neurons which form reflex arcs of various complexity, closing at different levels of central nervous system.

I—Region of spinal cord (or medulla oblongata); *II*—region of optic thalamus; *IIa*—region of nuclei of pallidal system; *IIb*—region of nuclei of midbrain, entering extrapyramidal system; *III*—cerebral cortex. Three nerve fibres marked *A* are afferent fibres extending from receptors and entering spinal cord or medulla oblongata (cell bodies which give off these fibres lie in spinal ganglia or in ganglia of craniocerebral nerves *S*). Diagram shows contact of these fibres with cells of spinal cord (or medulla oblongata), which by their axons form ascending pathways *(A_1)*, and with internuncial neurons (little black circles). Larger white circles A_1 and A_2 are nerve cells forming ascending afferent pathways by their axons: A_1, neurons whose axons conduct impulses to nuclei of optic thalamus; A_2, neurons whose cell bodies lie in region of optic thalamus, and whose axons terminate at A_3, cells of cerebral cortex. Little black circles show cell bodies of internuncial neurons of various parts of brain and spinal cord; axons and dendrites of these neurons do not go beyond corresponding part and form numerous connections. *E*, cells of cerebral cortex forming descending pyramidal pathway to terminal efferent neurons *(Eff.)*. E_I—cortical cells forming fibres which descend to cells of pallidal system (also connected with optic thalamus). Latter act upon terminal efferent neurons *(Eff.)* through efferent neurons *(E_{III})* of brain stem. *E.f.* fibres of efferent nerves. Ascending pathways are shown by solid lines; descending pathways, by dotted lines.

integral. Synaptic connections between the neurons ensure the relative autonomy of the neurons, which is inherent in any cell of the organism. But the same connections unite the neurons into a qualitatively new category and ensure the direction of the excitatory process in the nerve tissue."

Neurons Forming the Reflex Arc

Each reflex arc includes: 1) neurons giving off afferent fibres to the receptors, 2) neurons projecting efferent fibres to definite effectors, and 3) internuncial neurons connecting the afferent and efferent neurons.

Afferent neurons. All neurons whose axons connect the receptors with the central nervous system, thus forming afferent nerve fibres, are peripheral afferent neurons. Their cell bodies lie in the spinal ganglia or in homologous ganglia of the cranial nerves.* Each of the axons of these afferent neurons divides near the cell body into two branches: one of the branches extends to the receptor, the other enters the spinal cord (through the posterior roots) or the medulla oblongata.**

Some cell bodies of afferent neurons lie outside the spinal ganglia along the nerve trunks and in the nerve plexes of the internal organs. Some neurologists assume that a small number of the afferent fibres enters the spinal cord through the anterior roots.

The neurons of the central nervous system (Fig. 221) which form its ascending pathways (page 532) can be likewise regarded as inner-central afferent neurons; they also include the axons of the group of neurons of the optic thalamus (page 598) and the neurons which are situated in the cortex and at which the nerve fibres entering the cortex from the lower regions of the brain (mainly from the optic thalamus) terminate.

Efferent neurons. Neurons whose axons form effector nerve fibres connecting the central nervous system with the effectors, are terminal efferent neurons. They are called terminal because excitation arising in the centres is transmitted to the effectors only along the axons of these neurons.

The efferent neurons whose axons transmit impulses to the skeletal muscles producing contraction of the latter are called *motor neurons*, or *motoneurons*; the cell bodies of these neurons lie in the anterior horns of the grey matter of the spinal cord and in some nuclei of the medulla oblongata; their axons are motor nerve fibres. The axons of all other efferent neurons of the central nervous system form preganglionic fibres of the vegetative nervous system; the cell bodies of these neurons are situated in the lateral horns of the spinal cord, in the medulla oblongata (the nuclei of the V, VII and X pairs of cranial nerves) and in the midbrain (the nucleus of the III pair of nerves); the axons of these neurons terminate at the vegetative ganglia, at their cells giving off efferent (postganglionic) fibres.

Neurons whose axons form *descending* pathways of the central nervous system (fibres of the pyramidal and extrapyramidal system) are usually also regarded as efferent neurons (according to the nature of their function). Along the aforesaid pathways impulses from the higher parts of the brain are transmitted to the effector terminal neurons, i.e., to motoneurons, or neurons whose axons form preganglionic vegetative fibres.

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* The afferent fibres of the optic and olfactory nerves are of a special nature. These fibres are axons of nerve cells lying in the olfactory and visual receptors.

** At present many histologists designate as an axon of an afferent neuron only that branch of the neuron which extends from the place where the short process of the cells of the spinal ganglia branches out to the spinal cord (or medulla oblongata) and the other part of this process extending to the receptor as a dendrite. In this case only those fibres are designated as axons which transmit impulses from the body of the nerve cell, while the processes transmitting impulses to the body of the nerve cell are called dendrites.

Internuncial neurons. Internuncial neurons (Figs. 221 and 222) are neurons which have no direct connection with receptors or effectors and whose axons do not extend beyond this or other part of the central nervous system (spinal cord, medulla oblongata, midbrain, cerebellum, pallidal system, cerebral cortex); owing to this, they do not participate in the formation of long conducting pathways. All the internuncial neurons are receptive neurons (p. 525). They only differ from the neurons which may be termed intra-central afferent neurons (whose axons form ascending pathways of the central nervous system) in that the impulses arising in different groups of receptors can be conducted to them. In other words, their structural connections with the fibres, conducting impulses from various receptors, are not so firmly fixed as those of the neurons which form the conducting pathways. Most afferent fibres extending from the receptors do not directly contact the efferent neurons, but the internuncial neurons (and the neurons whose axons form *ascending pathways* of the spinal cord and medulla oblongata).

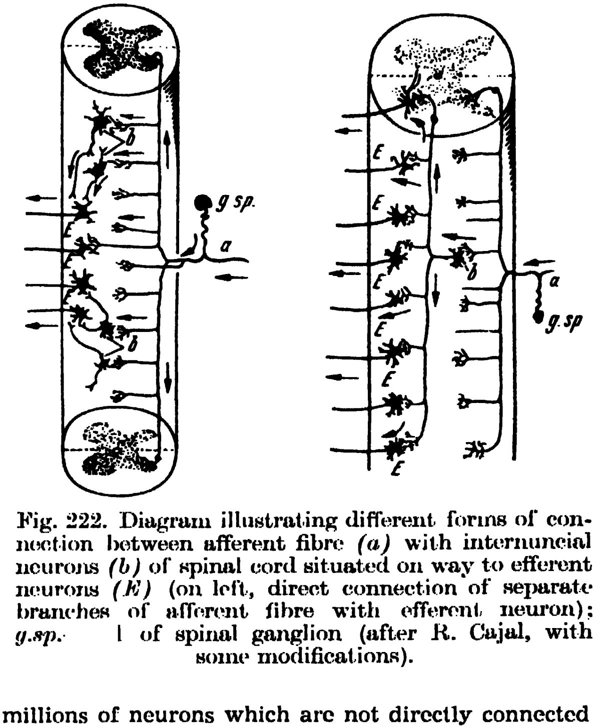


Fig. 222. Diagram illustrating different forms of connection between afferent fibre *(a)* with internuncial neurons *(b)* of spinal cord situated on way to efferent neurons *(E)* (on left, direct connection of separate branches of afferent fibre with efferent neuron); *g.sp.* l of spinal ganglion (after R. Cajal, with some modifications).

The number of all efferent fibres issuing from the central nervous system, and consequently of the efferent neurons, runs into hundreds of thousands. There are two to four times as many afferent fibres, and consequently afferent neurons, as there are efferent fibres and neurons. The total number of both is estimated at several million, while that of the nerve cells in the cerebral cortex alone is believed to run into 14 or 15,000 million. These figures—the thousands of millions of neurons which are not directly connected with effectors or receptors (compared with the several millions of afferent and efferent neurons)—convincingly demonstrate the significance of the internuncial neurons.

Connection between neurons in a reflex arc. Figs. 221 and 222 schematically illustrate the connections between the afferent fibres and the neurons of the central nervous system. The figures show the important fact that upon entering the spinal cord, the afferent fibres give off several branches, as a result of which *each afferent fibre establishes a synaptic connection not with one, but with several neurons* lying in the spinal cord or medulla oblongata.

The branches of afferent neurons terminate at the internuncial neurons, and not directly at the efferent neurons of the spinal cord and medulla oblongata (a probable exception is described on page 570). The axons of the internuncial neurons, in their turn, give off several little branches which terminate either on other internuncial neurons, or on efferent neurons. The scheme, according to which a reflex arc consists only of three neurons—afferent, internuncial and efferent—is far from corresponding to reality. A reflex arc may include two or more internuncial neurons; consequently, impulses from afferent fibres can spread along a number of pathways.

Axons forming the pathways of the central nervous system connect all of its structures, including the cerebral cortex. The great number of neurons of the cerebral cortex, the cerebellum and a number of nuclei of the diencephalon and midbrain may be regarded as aggregates of internuncial neurons superimposed on the lower divisions of the central nervous system; none of them, we repeat, are directly connected, through their axons, with either the receptors or the effectors.

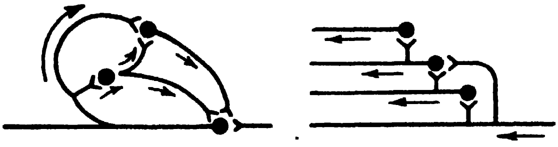


Fig. 223. Multiple (right) and closed (left) inclusion of various neurons into a reflex arc (after Lorente de Nó).

Connections between the neurons may be of the multiple chain (Fig. 223, right diagram) and the closed chain (Fig. 223, left diagram) types. In the latter case impulses arising under the action of afferent stimuli in definite neurons are transmitted through intra-central connections, formed by the processes of the axons, to the same neurons in which they originated. Owing to this, the excitation produced in the centres can be kept up by the circular movement of excitation along the cyclic system of the neurons. The circular movement of the excitation abruptly stops here when the circling excitation gets into the refractory phase created by the preceding impulse.

Reflex Activity and Humoral Factors

Concept of neurohumoral regulation. As before stated, in a number of cases changes in the composition of the blood bring about changes in the functions of the organism.

Such changes in the composition of the blood are caused: a) by the passage of tissue metabolites of any organs into the blood; some of these metabolites are formed continuously (for example, CO_2), others appear in large quantities only under special conditions, for example, in anoxia or during destruction (disintegration, necrosis) of various tissues; b) by the passage of hormones, formed in the endocrine glands, into the blood.

Changes in the composition of the blood upon entrance of certain substances into it may essentially alter a number of physiological processes. Suffice it to remember the action of carbon dioxide on respiration, the hormone of the posterior lobe of the hypophysis on the kidneys, hypoglycemia on the nervous system, etc.

The action of the substances carried by the blood (as well as by the lymph and cerebrospinal fluid), i.e., their *humoral* action, gave rise to the concept of the so-called *humoral regulation* of physiological functions. At first it helped in accumulating facts which showed the significance of chemical changes in the organism, but subsequently led to the idea of the supposedly *independent nature* of humoral regulation. Hence the erroneous *contraposition* of the action of humoral agents to the phenomena of reflex regulation. This system of views divorced the action of substances carried by the blood from the integral activity of the organism in its environment. The fact that the formation and influence of active chemical substances on various functions of the organism is always connected with the regulating influence of the central nervous system, was not sufficiently appreciated.

Actually, there is no independent humoral regulation as a closed group of separate, isolated phenomena, independent of reflex processes. The various active substances carried by the blood are, as a rule, only participants of reflex acts.

The dependence of the blood composition on reflex influences was discussed in Chapter 7. Characteristic examples are: reflex regulation of the content of sugar and water in the blood, and regulation of the entrance of hormones (adrenalin, thyroxin, insulin and pituitrin) into the blood.

Reflex mechanism of the action of humoral agents. All tissues and blood vessels have numerous osmoreceptors and chemoreceptors which are stimulated by carbon dioxide, oxygen deficiency, acetylcholine, histamine, changes in the osmotic properties of the blood and its ion composition (including changes in the concentration of H-ions) and certain drugs (for example, lobeline, camphor, etc.). Stimulation of receptors reflexly influences blood circulation, respiration and other processes in the organism. The reflexes produced by stimulation of chemoreceptors are, for example, respiratory changes caused by an accumulation of carbon dioxide in the blood and tissues and circulatory changes resulting from hypoxia. It is also probable that in the action of some hormones a certain part is played by reflexes resulting from the stimulation of chemoreceptors by hormones.

Direct action of various chemical substances on the central nervous system. As the most reactive structures of the organism, the nerve cells are highly sensitive to any changes in the composition of the surrounding medium. This is clear from the fact that the cells of the cerebral cortex are the first to react to oxygen and vitamin B deficiency, decrease in blood sugar, acidosis, etc.

In a number of cases the central nervous system reacts to considerable changes in the normal composition of the internal medium not by coordinated reflex acts, but either by a suppression of functions or by general excitation. For example, the direct action of oxygen deficiency in the blood on the respiratory centre causes paralysis of this centre. A decrease in the sugar content of the blood, if it directly influences the nervous centres, also deranges their coordinated activity and manifests itself in general convulsions.

Changes in the composition of the blood may greatly influence the excitability of the central nervous system. The effect of sexual hormones on the excitability of the reflex arcs of sexual reflexes is a good illustration.

Some substances, alien to the animal organism, stimulate definite structures of the central nervous system; owing to this, their introduction into the blood evokes coordinated acts. Apomorphine is one of these compounds; it provokes vomiting by its direct action on the vomiting centre (most of the other substances provoke vomiting through the stimulation of the receptors of the alimentary canal, i.e., reflexly). Hypnotics and certain febrifugal substances may also be regarded as agents which in a certain measure produce coordinated changes and which act electively on definite structures of the central nervous system. The paralyzing effect produced primarily on the cerebral cortex by the substances used in general anaesthesia (this narcosis usually being preceded by a phase of excitation) is of great practical importance.

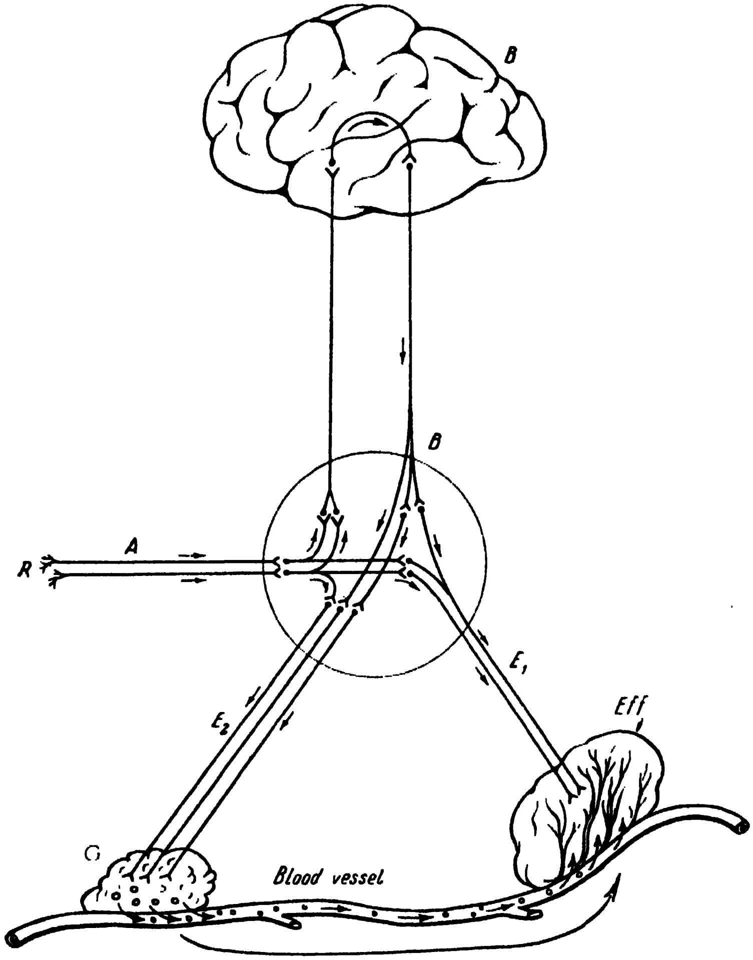
Participation of the humoral mechanism, as an intermediary link, in some reflex acts. Stimulation of any receptors may produce an unconditioned (and a conditioned) reflex excitation of the neurons which innervate a certain endocrine gland. This reflexly alters (increases or decreases) the passage of the hormone of the given gland into the blood; the action of this hormone on certain effectors modifies their activity. Instead of the chain:

receptor → afferent fibres → centre → efferent fibres → effector

we have the following chain:

receptor → afferent fibres → centre → efferent fibres → endocrinal gland
discharge of the hormone into the *blood → effector.*

This is schematically shown in Fig. 224.



g. 224. Diagram illustrating direct reflex influence on an organ *(Eff.)* and reflex-humoral influence, including a humoral link.

R, receptor; *A*, afferent nerve fibres; *B* region of lower divisions of central nervous system where afferent impulses can be switched over both to efferent neurons *(E_1)* directly innervating effector *(Eff.)*, and efferent fibres *(E_2)* acting upon endocrine gland *(G)*, whose hormone is carried by blood along blood vessels to effector, thus modifying its activity. Arrows show possible ways of propagation of impulses from receptor to higher parts of brain *(B)* in which these impulses can be transferred both to E_1 and E_2, owing to elaboration of conditioned reflexes.

The reflex neurohumoral regulation of the function of the kidneys described on page 406 is a typical example of a reflex act, whose efferent link includes production of hormones. A similar example is offered by the increase in the sugar content of the blood during strenuous work, the increase caused by reflex stimulation of the secretion of adrenalin and the subsequent breakdown of liver glycogen due to the action of adrenalin. The heightened secretion of thyroxin, the hormone which intensifies the exchange of energy, is also a reflex response of the thyroid gland to the cooling of the body.

Reflexes having an efferent humoral link may be both unconditioned and conditioned reflexes. The latter are involved in complex reflex acts peculiar to each activity of the organism.

The humoral link involved in the accomplishment of reflexes may even consist of two components; for example, certain hormones of the hypophysis humorally affect other endocrine glands (sexual and thyroid glands). The following pathway of a reflex is therefore also possible:

receptor → afferent fibre → centre → efferent fibre to the hypophysis → action of the hypophyseal hormone through the blood on the gland n → action of the hormone of the gland n through the blood on the effector.

The facts demonstrating the participation of the humoral (hormonal) link in the accomplishment of certain reflexes warrant the assumption of a reflex nature of the phenomena which proceed so slowly that no direct nervous influences upon them have as yet been discovered. But considering the reflex mechanism of the action of humoral agents we can speak not only of the reflex regulation of diuresis, the sugar content in the blood or thermoregulation (which has become almost universally recognized), but also of a similar regulation of growth (through the reflex stimulation mainly of the hypophysis and the thyroid), regulation of sexual maturation, reflex nature of the involution of the thymus, reflex nature of obesity, etc.; consequently, we can see in all these effects the influence of the external and internal environment which is exerted upon them through the nervous system.

The above facts show that the action of various chemical substances is never isolated from the reflex activity: humoral factors are always included in the integrated complex of reflex activity.

Even the influence of internal chemical changes on the chemical processes themselves, for example, on the enzymic systems of different peripheral tissues, also depends on the state of the tissues, which is determined by nervous, i.e., reflex actions. The possibility of elaborating a conditioned reflex to metabolic changes provoked by the introduction of thyroxin clearly shows the importance of the nervous system even in such seemingly purely chemical processes.

Influence of the State of Effectors on the Nature of Reflexes

The nature of a reflex may very largely depend on the state of the effectors. For example, when the skeletal muscles become fatigued, their response to impulses from motoneurons may change and their contractions weaken. When the blood circulation in some organ is impaired, this organ often does not react to impulses transmitted to it from the centres.

Changes in the functional state of the effectors affecting their reflex acts are often themselves conditioned by a reflex mechanism, and result from the stimulation of receptors residing in the same effectors. For example, muscle fatigue is to a considerable extent caused by impulses arising in the receptors of the contracting muscles. The same is true for respiratory changes resulting from pathological processes in the pleura or abdominal cavity, changes in the micturition reflex after operations on the abdominal cavity, etc.

Peripheral Nervous Regulation

Reflexes are usually defined as reactions of the organism to the stimulation of receptors necessarily involving the central nervous system. It is therefore impossible to regard the manifestations of the nerve structures situated outside the central nervous system as true reflexes. There are reactions, however, which are produced by the stimulation of receptors and which depend on reflection of the nervous excitation on the effectors outside the central nervous system; the term "peripheral reflexes" may be applied to these reactions.

Axon-reflexes. Axon-reflexes signify reactions of various effectors produced by the propagation of impulses from the receptors along the branches of the axon of the afferent nerve fibre. They were first described by N. Sokovnin (1874), who showed that stimulation of the central section of the hypogastric nerve produced a contraction of the urinary bladder even when the connection of this nerve with the spinal cord was disrupted. Subsequently, reactions which may be regarded as resulting from the conduction of impulses along the axon branchings of one neuron, were described (Bayliss, Langley et al.) in the activity of the heart, the blood vessels (p. 153) and other organs.

Some researchers doubt the existence of axon-reflexes and regard all the phenomena described under this term as conditioned only by the synaptic peripheral transmission of impulses from an afferent to an efferent neuron. The morphological investigations of B. Lavrentyev and his pupils, however, proved that afferent fibres extending from the receptors often gave off a branch which terminated on the smooth muscles and in the connective tissue surrounding the capillaries. Consequently, impulses of excitation arising in the afferent fibre as a result of the stimulation of the receptors may be transmitted within this neuron to its branches extending to the effectors. It is probable that the reaction of the latter depends on the secretion of particularly active substances (for example, acetylcholine, histamine) in the endings of the afferent fibre.

The characteristic feature of the axon-reflexes is that they are effected through the conduction of excitation *within one neuron*; the branch of the afferent fibre leading to the effector functions as an efferent fibre. Axon-reflexes do not disappear after the removal of the spinal cord. When the afferent fibres are sectioned distally to the spinal ganglia, but above the site where the afferent fibre branches out, the axon-reflexes disappear only after degeneration of the axons.

Peripheral synaptic transmission of excitation from afferent to efferent neurons. In addition to the axon-reflexes, by which impulses are transmitted from the receptors to the effectors within one neuron (that is, without passing through any synapse between the neurons), impulses are also conducted along the chain of neurons which do not enter the central nervous system.

A considerable number of nerve cells (described by Dogiel, Ivanov, Saburov, Lavrentyev et al.) is found in various organs (for example, the heart, intestinal tract, stomach and blood vessels). These cells situated in the intestinal tract and in the heart are often regarded as cells whose axons form postganglionic parasympathetic fibres, i.e., only as links in the transmission of excitation by way of the parasympathetic nervous system. It is hardly correct, however, to ascribe to all the nerve cells situated in the walls of various organs the role of mere intermediate points for impulses which come to them from the nerve centres. A. Dogiel has long since discovered (1895) that the sympathetic ganglia contain, in addition to the cell bodies of the efferent neurons (designated as Dogiel cells, type I), cells which were subsequently given the name of Dogiel cells, type II. They are afferent neurons whose axons terminate in the cells of type I, and whose long dendrites form receptor apparatuses. Dogiel cells, type II, i.e., afferent neurons, have been discovered in a number of blood vessels, in the intestinal tract, and in the stomach.

Thus, microscopic anatomy has established the possibility of existence of a reflex arc in which the contact between the afferent and efferent neurons is effected outside the central nervous system—in the intramural ganglia of the intestinal tract, the sympathetic ganglia, the walls of the blood vessels and the tissues that surround them. This is also demonstrated by a number of physiological facts. For example, if the organs of the abdominal cavity (Y. Sinelnikov) and of the blood vessels are separated (Konradi) from the central nervous system, they exhibit responses to the stimulation of receptors which can hardly be regarded as axon-reflexes. Distention of the rectum, for example, produces a contraction of the uterus and of the urinary bladder even when all these organs are extirpated from the body and placed in a warm saline bath (Sinelnikov).

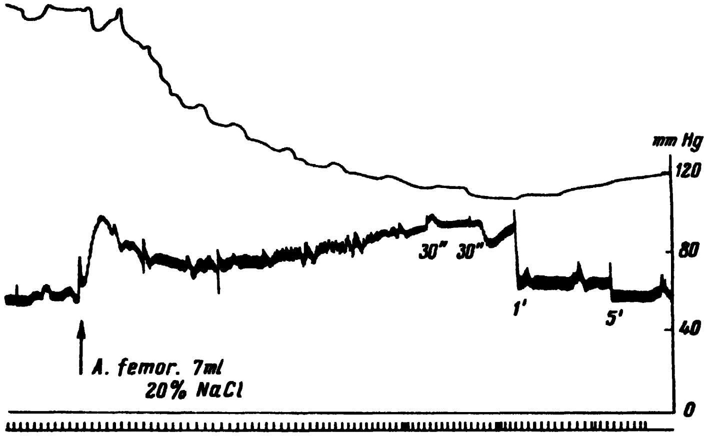


Fig. 225. Peripheral vascular reactions to injection (arrow) of a 20% solution of NaCl into the femoral arteries.

Top to bottom: record of change in volume of spleen denervated 6 days before experiment; record of arterial pressure; zero line of pressure and time intervals (in seconds). Experiment performed one hour after removal of entire spinal cord of the dog below cervical segments.

Any action upon the vascular network of the arterial system, for example, a dilatation of the arteries by a rapid injection of Ringer's solution or a concentrated solution of sodium chloride into them produces a considerable increase in the vascular tone which manifests itself in a heightened arterial pressure, even after the complete removal of the spinal cord (Fig. 225); this reaction disappears after introduction into the blood vessels of a solution of novocain, a substance which does not decrease the reaction of the vascular muscles to adrenalin and barium chloride, i.e., does not directly affect the smooth muscles of the blood vessels. This warrants the assumption that the vascular reactions to dilatation or chemical stimulation of the arteries are produced by the stimulation of receptors; at the same time the persistence of these reactions for a period of 7 to 10 days after the severance of all nerves running to the given vascular area does not permit to regard them as axon-reflexes. Similarly, the reactions of the muscles of the intestinal tract to stimulation of its mechanoreceptors are almost undoubtedly due to the transmission of excitation from the afferent to the efferent neuron in the intramural plexus of the wall of the intestinal tract.

The problem of peripheral reflexes has been studied but little. In addition to the aforesaid cases, these reflexes were also described for the secretory activity of the cutaneous glands, for the regulation of pressure in the eye and for the contraction of the urinary bladder. Pavlov was inclined to ascribe an important role to peripheral reflexes, believing them to determine the secretion of milk and pancreatic juice after denervation of the mammary and pancreatic glands. It should also be remembered that the automatism of the cardiac and smooth muscles may be hypothetically regarded as involving the peripheral reflexes effected by the neurons of Remak's, Bidder's, Dogiel's and Ludwig's ganglia in the heart and by the neurons of Auerbach's and Meissner's plexes in the intestinal tract.

The activity of the peripheral nerve structures cannot be independent of the influence of the central nervous system upon them. This question, however, is not clear as yet.

CHAPTER 53

CHARACTERISTICS OF THE EXCITATORY PROCESSES IN THE CENTRAL NERVOUS SYSTEM

Nature of Afferent Impulses Acting Upon the Central Nervous System

The nature of the impulses transmitted to the centres from the receptors along afferent nerve fibres is studied by means of recording the action currents which arise in these fibres during stimulation of the receptors (Adrian). It has been shown that excitation is always conducted along afferent fibres as separate impulses. These impulses follow one another at different frequencies which normally vary from 3 or 4 to 200 per second. The impulses in the receptors arise intermittently even under continuous stimulation.

The more intense the stimulation of the receptor, the more frequent the excitatory impulses arising in it.

Certain facts (A. Speransky) warrant the assumption that not only rapidly spreading impulses can be transmitted from the receptors to the centres; it is probable that some peculiar effects on the nerve, similar to those described by Wedensky under the term perielectrotonus, are transmitted from the receptors. However, only separate facts concerning this subject are available, and even they have not yet been sufficiently analysed.

Specific Features of Conduction of Excitation Through the Centres

Nervous impulses resulting from the stimulation of receptors in the afferent nerve fibres act upon those cells in the central nervous system at whose surface the given afferent fibres terminate. The excitation produced by the impulses from the afferent fibres in these nerve cells is transmitted along their axons, which spread within the central nervous system, and, in its turn, acts upon the new groups of neurons with which these axons come in synaptic contact. Being thus transmitted within the central nervous system from one group of neurons to another, excitation (or inhibition, see Chapter 54) in the end passes over to definite efferent neurons of the final common path, and then spreads along their axons to the effectors. Consequently, *in each reflex nervous impulses are transmitted across synapses from one neuron to another.* The study of impulse transmission across synapses is, therefore, important for the comprehension of reflex activity.

One-way conduction of impulses across the synapses. Impulses of excitation travelling along nerve fibres can spread in both directions from the point of stimulation; but in the central nervous system they usually spread only in the direction from the afferent to the efferent neurons. This means that in the central nervous system the impulses are transmitted only from the axon of one neuron to the cell body and dendrites of other neurons and are not transmitted from the dendrites and body of the nerve cell to the branchings of the axon extended to them.

However, the one-way synaptic conduction of impulses should not be considered an absolute principle. In the cerebral cortex impulses can, apparently, be transmitted in all directions—not only from the axons of one neuron to the body and dendrites of another, but also from the dendrites and body of a nerve cell to the axon endings extended to them.

Rate of conduction of impulses across synapses. Transmission of a nervous impulse from one neuron to another requires a certain time. This can be demonstrated by measuring the total reflex time, i.e., the time which passes between the application of a stimulus to the receptor (or to the afferent fibres), and the beginning of the reflex activity of the effector. The total duration consists of: 1) the time required for the excitation of the receptors and for the conduction of impulses along the afferent fibres to the centre; 2) the time for the spread of excitation through the centres; 3) the time for the propagation of impulses along the efferent fibres to the working organ; 4) the latent period of the working organ. By subtracting from the total reflex time the time spent on the processes indicated under 1, 3 and 4, we can find the so-called reduced time of a reflex, i.e., the time excitation travels through the centres. The conduction of excitation through the centres appears to require in some "simple" reflexes from one to three m/sec., and sometimes even 0.7 m/sec. which is still longer than the time required for the conduction of impulses through a similarly long homogeneous conductor. A so-called "central delay" occurs, which testifies to the fact that a certain time is required for the passage of excitation from an afferent to an efferent neuron.

More accurate results can be obtained by measuring the interval between the application of an induction shock to the afferent fibres where they enter the brain and the emergence of a bio-electric current which is an electric index of the reflex response in the efferent fibres at the point where the anterior root arises.

The central delay is probably the longer, the greater the number of neurons through which the impulses of excitation pass in the central nervous system. Simple reflexes (tendon reflexes, the flexor reflex) therefore take several milliseconds and even fractions of a millisecond, more complex reflexes with a long reflex arc take 10 to 20 milliseconds, while reflexes involving the cerebral cortex take up to 0.5 second (500 milliseconds). The longer reflex time is due mainly to the development of inhibition in certain neurons of the reflex arc.

Summation of impulses in the nerve centres. In a nerve fibre a single stimulus (if it is not subliminal or supramaximal) produces one excitatory impulse. But in the centres, as was first shown by I. Sechenov, a single impulse arising in the afferent fibres usually produces no reflex excitation, i.e., it is not transmitted to the efferent neurons. To produce a reflex requires several successive stimuli to the afferent fibres.

Each individual impulse in a nerve fibre produces a local change in the superficial layer of the nerve cell at which the branches of the given fibre terminate. This local change is manifested in a transitory increase in excitability and may be designated as a state of local subliminal excitation, which is believed to be confined to the area of the synapse and to become extinct 1 to 2 m/sec. after its emergence. If within this time a second impulse acts upon the same area, excitability in the region of the given synapse will increase still more. Growing more intense with each successive impulse local excitation will reach a state in which any subsequent impulse entering the area of contact between the axon and the cell body will no longer produce a local increase in excitability, but a discharge of excitation which will embrace the whole nerve cell and spread to its branches.

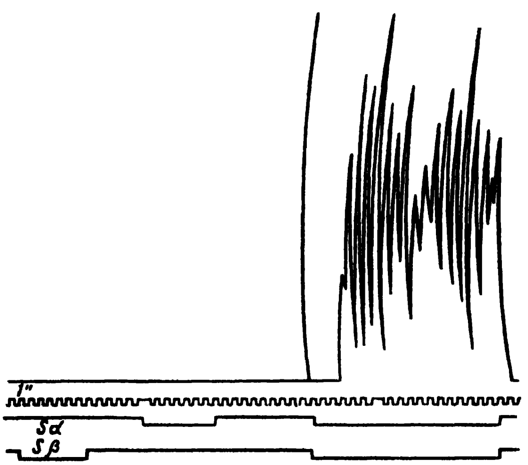


Fig. 226. Summation of stimuli in central structures of reflex arc.

Two stimuli, separately applied to different areas of the skin (drop of lines $S\alpha$ and $S\beta$), produce no reflex. Two stimuli applied simultaneously produce strong response (upper recording) scratching reflex (after Sherrington).

Since several afferent fibres are usually stimulated simultaneously, the impulses coming to the centre along various afferent fibres and acting upon the same neuron can be summated. An impulse which comes from one of the afferent fibres to the synapse somewhat later than an impulse from another afferent fibre (or simultaneously with it) finds production of excitation facilitated. For example, separate weak stimulations of two areas of the skin on the back of the dog with a severed spinal cord produce no rhythmic flexion and extension of the paw; but the same stimulations applied simultaneously, produce a strongly pronounced reflex (Fig. 226).

Successive excitation in the centres. In the nerve centres, unlike the nerve fibres, excitation often persists for some time *after* stimulation of the receptors or the afferent fibres has been discontinued (*successive excitation* of the centres). (Fig. 227.)

Rhythm, strength and duration of reflex responses. From the foregoing it follows that: 1) excitation in various central neurons does not arise strictly simultaneously; 2) not every single afferent impulse produces impulses in the efferent neuron; 3) flashes of excitation in the centres may arise some time after discontinuance of the stimulation of receptors. As a result the nature and frequency of nervous impulses in the efferent fibres often do not in the least reflect the nature of the afferent impulses.

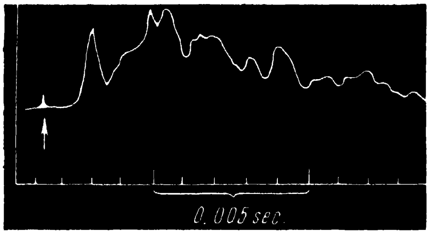


Fig. 227. Record of bio-electrical currents of anterior spinal root in response to single stimulation of posterior root (arrow) of same segment. Time interval (0.001 second) shown below. Record shows plurality of responsive impulses evoked by single stimulation of posterior root, and short duration of transmission of impulse through centres. Rise of curve at moment of stimulation marked by arrow is due to ramification of stimulating current (after Lloyd).

Fig. 228 shows a recording of the contraction of *m. tibialis* in a spinal cat in response to a maximal single stimulation of the motor nerve (lower curve), to a maximal, also single, stimulation of afferent fibres in *popliteal nerve* (upper curve). In the latter case we see a pronounced and rather persisting tetanus, which testifies to the fact that a number of successive efferent impulses arising in the centre in response to a single stimulation of the afferent fibres come from the centre along the motor nerve to the muscle when it is in a state of *reflex* excitation. Consequently, the centres are characterized by their ability to transform the rhythm of afferent impulses acting upon them into a different, "central" rhythm.

The frequency of impulses arising in the efferent neurons in normal activity usually varies from 4 and 10 to 30 and 70 per second. The strength of the reaction of the effector is generally determined (other things being equal) by: a) the frequency and nature of impulses in each efferent fibre; b) the number of excited efferent neurons; c) the degree of synchroneity, i.e., simultaneity of the impulses which reflexly arise in the efferent neurons governing the given effector.

Synchronous excitation in the neurons of a given final common path excites more contracting (or secretory) elements of the working organ per unit of time. If impulses of excitation do not arise in the central neurons synchronously, the reaction of the effector weakens at every given moment and the working cells continuously replace each other (asynchronous excitation is often likened to running fire, while excitation arising simultaneously in all the efferent neurons of the given organ is likened to a volley).

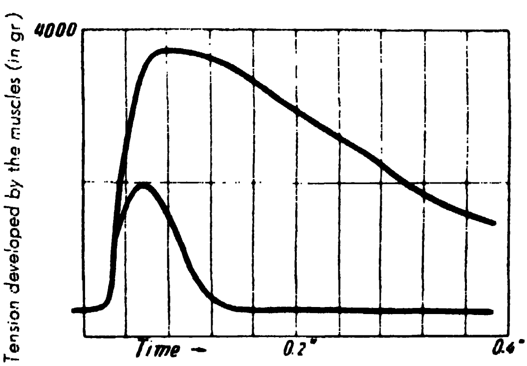


Fig. 228. Upper curve: reflex contraction of m. tibialis ant. under stimulation of popliteal nerve on same side by single strong induction shock. Lower curve: contraction of same muscle in response to single maximal stimulation of motor nerve (after Denny-Brown, Creed, Liddell and Sherrington).

Fatigability of the nervous centres. Under tetanic stimulation of an afferent nerve the reflex contraction of muscles produced by this stimulation is extinguished within several minutes (Fig. 229). Stimulation transferred to another afferent nerve restores the reflex contraction (Wedensky). It follows that fatigue develops in the internuncial neurons; should the efferent neuron be fatigued the transfer of stimulation to another afferent nerve could not restore the reflex contraction.

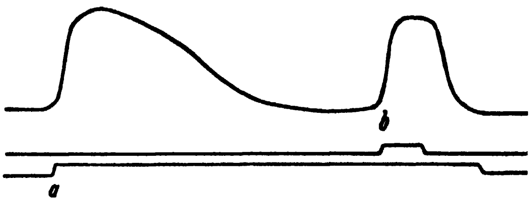


Fig. 229. Line *a* shows the stimulation of one afferent nerve which reflexly produces contraction of muscle. When this contraction disappears ("fatigue" in central neurons) another afferent nerve (mark *b*) is stimulated. Reflex contraction of muscle at once recovers (after A. Ukhtomsky).

Action currents in the nervous centres. Action currents in the nervous centres are distinguished for the long duration of the electrical potentials arising after each flash of excitation in these centres. The nervous centres often show protracted residual electronegativity and a still more protracted positive aftereffect (Fig. 230). There are reasons to believe that the phase of residual electronegativity corresponds to the state of heightened excitability of the central neurons, and the phase of residual electropositivity to their lowered excitability (Gasser).

Metabolism in the nervous centres and the influence of certain poisons upon them. Metabolism in the nerve cells is higher than in nerve fibres. If the nerve cells lack oxygen (for example, when the flow of blood to them ceases) they soon lose their excitability and die.

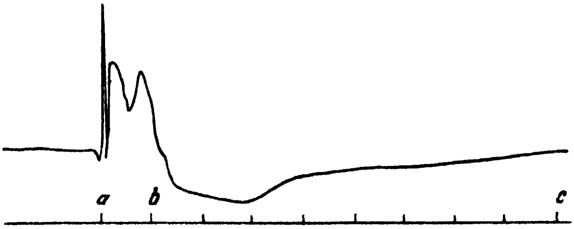


Fig. 230. Modification of electric potentials of spinal cord in response to single stimulation of posterior root.

spike, residual electronegativity from *a* to *b* and positive aftereffect from *b* to *c*. Time interval, 0.01 second (after Gasser).

In active nervous centres the metabolism increases; under reflex excitation of the spinal cord 3 to 4 times as much oxygen is consumed as at rest. Consumption of sugar and formation of CO_2 also increase. Acetylcholine is apparently formed (or liberated from some other compound) in the nerve cells or in the endings of the axons.

The nerve centres are paralyzed by anaesthetics (ether, chloroform, etc.) more easily than any other tissues.

The specific features of conduction of excitation through nervous centres and along nerves are summarized below:

Nerve fibres	Nervous centres
1. Conduct excitatory impulses in both directions	1. Conduct excitatory impulses only from the afferent to the efferent neurons
2. An impulse is conducted at the same rate along the entire fibre	2. The conduction of impulses involves a certain delay
3. The processes of summation are imperceptible; nervous impulses arise at each threshold stimulation	3. The processes of summation are strongly pronounced; each afferent impulse produces a flash of excitation usually only under conditions of heightened excitability resulting from the action of the preceding impulse
4. The rhythm of impulses, even at their high frequency (500 to 1,000 per second), conforms to the rhythm of the stimulations (minor transformation of the rhythm)	4. The rhythm of reflex discharges in the efferent neuron often does not conform to the rhythm of afferent impulses (strongly pronounced transformation of impulses)
5. When stimulation is not very strong the impulses of excitation cease as soon as stimulation is discontinued	5. Impulses of excitation very often continue to emerge after the discontinuance of stimulation of the afferent pathway
6. All changes taking place under excitation develop and disappear rapidly; thus the preceding activity of the nerve fibre hardly affects its excitability	6. The aftereffect of the preceding activity of the nervous centres is quite appreciable; the excitability changes easily
7. Metabolism is low	7. Metabolism is high
8. Practically indefatigable	8. Under frequently repeated stimulation become easily fatigued
9. Inhibition in the nerve fibre arises only under artificial stimulation	9. Inhibition is a characteristic factor in the activity of the nervous centres

Mechanism of the Synaptic Transmission of Excitation

Modern science does not as yet precisely know even the mechanism of propagation of excitation over so homogeneous a conductor as the nerve fibre. It is therefore the more difficult to explain the processes which determine and characterize the transmission of nerve impulses from one neuron to another in the central nervous system, this most complex organ of the animal, and we have only rather hypothetic ideas about the phenomena developing in the synapses during transmission of nerve impulses. These ideas about synaptic transmission of excitation in the centres are based almost entirely on theories substantiated by experiments performed on the nerve fibre and myoneural synapse.

As before stated (Chapter 49), the most elaborate theory today regards conduction of a nerve impulse as a result of the stimulating influence exerted on an unexcited portion of the nerve fibre by the potential difference between the excited and unexcited areas. This potential difference gives rise to a local current which within the nerve is directed from the excited to the unexcited portion. In the resting portion of the nerve, adjacent to the excited portion, there arises a negative pole of this local current which stimulates the resting area and excites it.

It is assumed that excitation of the neuron by impulses transmitted to its body and to the dendrites of the axon of another neuron requires a certain potential difference in the region of the synapses. When this potential difference reaches certain threshold value, the local subthreshold excitation in the region of the synapses is converted into an impulse of excitation embracing the whole cell and spreading along its entire axon. From this point of view the transfer of excitation from one neuron to another is determined by the threshold value of the electric potential in the region of the synapses and the conditions under which the potential emerges.

This very schematically described theory seems correctly to appraise the electric phenomena that arise during the activity of the nerve tissue. It is still unable, however, to answer a number of very important questions, for example, the reasons for the specific activity of various structures of the central nervous system and the nature of protracted aftereffects produced by excitation in the nerve centres.

Transmission of excitation from one neuron to another is conveniently studied on the ganglia of the sympathetic nervous system. Here the relations are somewhat simpler than in the nervous centres, since there are fewer neurons and interneuron connections in the ganglia than in any structure of the central nervous system. As in the centres, much more persistent after-potentials are observed in excited ganglia than in the nerve; these are attended by protracted (up to one-fifth of a second) changes in excitability apparent after each impulse of excitation. It has also been found that impulses of excitation continue to arise in the ganglia for some time after discontinuance of the rhythmic stimulation of the preganglionic nerve fibres. Lastly, perfusion of the cervical sympathetic ganglion and the study of the composition of the fluid flowing off from the ganglion have shown (Kibyakov) that during the transmission of excitation through the ganglion the latter liberates acetylcholine; this fact has been repeatedly confirmed.

Highly active compounds—acetylcholine and, probably, adrenalin—are also liberated in the central nervous system during its reflex activity. This was demonstrated by a study of the blood flowing off from the brain during stimulation of the afferent fibres of the vagus and aortic nerves (Konradi and Mikhelson).

Of course, the formation of acetylcholine in the nerve cells or in the region of the synaptic endings does not cover the whole cycle of biochemical and physicochemical transformations characteristic of the activity of the central nervous system, but represents an indispensable link in the chain of processes determining the transmission of excitation from one neuron to another.

Irradiation of Excitation in the Central Nervous System and Generalization of Reflexes

Excitation reaching the nervous centres along afferent fibres can be transmitted across a larger or smaller number of internuncial neurons to any structure of the central nervous system; the mutual disposition of the neurons does not alone predetermine the pathway along which excitation is propagated in the central nervous system. This is manifested in the so-called irradiation of excitation, in which excitation spreading widely over the central nervous system leads to generalized reflexes and involves effectors which normally do not react to the stimulation of the receptors.

Generalization of reflexes in the embryonic period. Extensive irradiation of excitation over the central nervous system is characteristic of one of the periods in its embryonic development. In this period stimulation of each group of receptors provokes general convulsions, i.e., simultaneous contraction of the entire musculature. Only later does the embryo begin to exhibit differentiated reflexes typical of a normal organism, for example, to jerk back only the stimulated leg when one of its toes is pinched, to respond with sucking movements to stimulation of the lips, etc.

The generalization of reflexes manifests itself in miscarried human foetuses. Its traces are also observed in normally born babies: during the first and second weeks of life they react with sucking movements not only to stimulation of the receptors of the lips, but also to that of the cheeks, chin and neck.

We shall see later that at the first stage of its formation each conditioned reflex is a generalized reflex. The process of delimiting the conditioned reflexes by which each of them is reproduced only in response to a limited group of stimuli, externally resembles the process of delimiting the unconditioned reflexes during the phylogenetic and ontogenetic development.

Generalization of reflexes in strychnine intoxication. After administration of a toxic dose of strychnine to an animal, any stimulation of the receptors, for example, a touch of the skin or a strong sound, provokes a contraction of the musculature of the whole body, i.e., convulsions. Excitation irradiates here over the entire central nervous system and results in simultaneous activity of a mass of motoneurons. The convulsions are a manifestation of this uncoordinated irradiation of excitation almost to all efferent neurons.

Manifestations of the generalization of reflexes under intensified stimulations of the receptors. A certain generalization of reflexes is also observed under increased stimulation of the receptors (until the strength of stimulation reaches a point beyond which comes inhibition) (page 549). For example, in decerebrate animals, weak or moderate stimulation of the afferent fibres, which extend from the receptors of the foot, results only in flexion of the stimulated extremity and extension of the symmetric extremity. But strong stimulation produces flexion of both legs; it may be accompanied by an upward movement of the tail, a movement of the forelegs and of the entire body.

Transmission of excitation from one neuron to another underlies the entire reflex activity. If nothing restricted irradiation of excitation from neuron to neuron, however, excitation would irradiate to all efferent neurons in response to any stimulation of the receptors, as in the case of strychnine intoxication. The reflex acts, by which the organism adapts itself to the stimulations that produce them, are therefore only possible because irradiation of the excitatory process over the central nervous system is circumscribed. This is accomplished by inhibition, a process which opposes the spread of excitation. An evaluation of its role requires thorough knowledge of coordination of reflex activity.

CHAPTER 54

COORDINATION OF REFLEX ACTIVITY AND PHENOMENA OF CENTRAL INHIBITION

Concept of Coordination of Reflexes and Its Biological Significance

Coordination of reflex activity signifies a complex of processes which ensure the accomplishment of definite acts in response to the stimulation of definite receptors.

Pavlov emphasized that reflex activity ensured a constant equilibration of the organism with all the conditions affecting it and interpreted the terms "expedience" and "adaptation" in the light of Darwin's evolutionary theory regarding the adaptive nature of the reflexes as an unquestionable fact. This adaptive significance of the reflexes is revealed in each normal reflex act. It is testified to, for example, by the contraction of the pupil under the influence of light, drop in the blood pressure in response to its increase, contraction of the urinary bladder as a reaction to its distention, secretion of digestive juices under the action of alimentary stimuli, etc.

The coordination of the reflexes is deranged if the response involves effectors whose activity does not contribute to the result attained by the elaborated reflex act.

The coordination of reflex activity is also expressed in the correspondence of the strength of the reaction to the strength of the stimulation by which it is produced and in the successive inclusion of various effectors in the reaction.

The reaction of the effectors to the stimulation of receptors is determined by the efferent neurons in which excitation arises as a result of the processes developing in the central nervous system under the action of impulses from the receptors. So long as the excitation (or inhibition) of the nervous centres does not reach the efferent neurons (Sherrington's final common path), it cannot make the organism react. But if the spreading excitation arises in the cell bodies of the efferent neurons, it influences, as a rule, the activity of the organs innervated by these neurons. For example, a reflex flexion of the fingers can be effected only when excitation embraces the neurons which innervate the common flexor of the fingers; there is no reflex secretion of gastric juice until excitation arises in the neurons of the nucleus of the vagus which innervate the gastric glands.

Consequently, each reflex is characterized by a definite distribution of excitation in the efferent neurons.

The inclusion of very definite neurons into each reflex arc is due to the fact that in the function of the central nervous system, which is determined by the conditions of life of the given species and each individual, the irradiation of excitation is limited by the process of inhibition.

Discovery of Phenomena of Inhibition in the Nervous Centres

In the nerve tissue inhibition manifests itself in a suppression of excitation or decrease in excitability and conductivity; inhibited nervous structures do not propagate excitation.

Phenomena of inhibition in the nervous centres were first discovered by Sechenov in 1862. This discovery was as important for the development of physiology as the formulation of the concept of reflex, since all normal nervous acts without any exception necessarily involve inhibition.

The famous Sechenov experiment consists in the following. If a leg of the frog whose cerebral hemispheres have been removed is immersed in a weak acid solution the frog jerks its leg out. The time which elapses between the immersion of the leg in the acid and its jerk out of the stimulating solution is the index of excitability of the neurons forming the reflex arc of the flexor reflex. Sechenov decided to find out whether stimulation of any parts of the frog's brain would produce a delay in the spinal reflexes similar to the inhibition of the heart contraction during stimulation of the vagi. Consequently, Sechenov's experiments represented a purposeful search for phenomena of inhibition in the nervous centres. In the course of these investigations Sechenov discovered that if a chemical stimulus—a crystal of sodium chloride—acted on the region of the optic thalamus (Fig. 231), the interval between the immersion of the frog's leg in the acid solution and the moment the leg was jerked out was several times as long. Consequently, stimulation of the optic thalamus inhibited the flexor reflex.

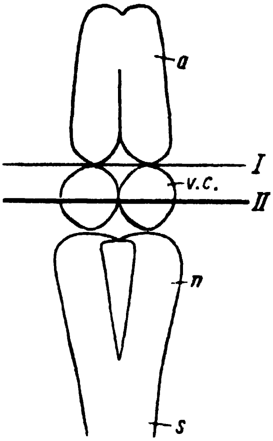


Fig. 231. Brain of frog (diagram).

Application of crystal of rock-salt to surface of cut made along line *II* sharply prolonged reflex tim[illegible]rebral hemispheres with olfactory lobes; *v. c.*— visual chambers; *n*— medulla oblongata; *s*— spinal cord (after I. Sechenov).

Phenomena of inhibition were later also observed by Sechenov himself, Spiro, Wedensky, Bubnov, Goltz, Sherrington, Samoilov, Ukhtomsky, Pavlov and his school, and other investigators.

We do not as yet know the nature of the inhibitory processes, i.e., the nature of the chemical and physicochemical processes in the nervous tissue which determine inhibition. Pavlov indicated, however, that in their physicochemical essence all forms of inhibition probably represented the same process, only arising under different conditions.

Simultaneous Inhibition of Some Nervous Structures and Excitation of Others (Reciprocal Inhibition)

Inhibition in the arc of one reflex may be produced by excitation in the arc of another reflex. For example, the flexor reflex in response to the immersion of the frog's leg in acid is inhibited if a strong mechanical or electric stimulus is simultaneously applied to the receptors of another leg. The swallowing reflex inhibits the inspiratory reflex. Salivation, reflexly produced from the taste receptors, is inhibited by any strong, noxious stimulation which provokes the defensive reflex. This group of phenomena also includes the so-called external inhibition of conditioned reflexes (Chapter 61). In all these cases one reflex inhibits other reflexes. This proposition, however, should not be made a general rule.

Each reflex involves very definite effectors. All effectors whose activity might impede the result attained under a certain reflex, are antagonists of the effectors which accomplish the given reflex. Consequently, reflexes leading to the activity of antagonistic effectors are antagonistic themselves. For example, under certain conditions and at a certain stage of its accomplishment the flexor reflex of an extremity becomes antagonistic to the extensor reflex. Similarly, the swallowing reflex is the antagonist of the inspiratory reflex.

When a certain coordinated act is performed, all reflexes antagonistic to it are inhibited. This inhibition clearly manifests itself when, during the accomplishment of one reflex, the receptive zone of the antagonistic reflex is stimulated. For example, during the accomplishment of the flexor reflex it is impossible to produce the extensor reflex by stimulation strong enough to produce the extensor reflex when there is no flexion. But if the extensor reflex is produced by increased stimulation of its receptive zone despite the flexion of the leg, the flexor reflex is inhibited (i.e., it disappears, or considerably weakens).

Fig. 232 shows a record of the contraction of two antagonistic muscles of the thigh—the flexor and the extensor—in the cat whose cerebral hemispheres have been removed. The rise of the second curve from below coincides with the moment when stimulation of the nerve which produces the flexor reflex has begun. The flexor contracts reflexly while its antagonist, the extensor, relaxes. This relaxation is accounted for by the fact that the neurons innervating the extensor muscles are inhibited as a result of the excitation of the centre of reflexion. Before the flexion began, during "rest," the extensor had been in a state of prolonged weak excitation leading to its prolonged weak contraction. The extensor had consequently been in a state of *tonic* excitation. This tone of the extensor was maintained by the impulses of excitation arising

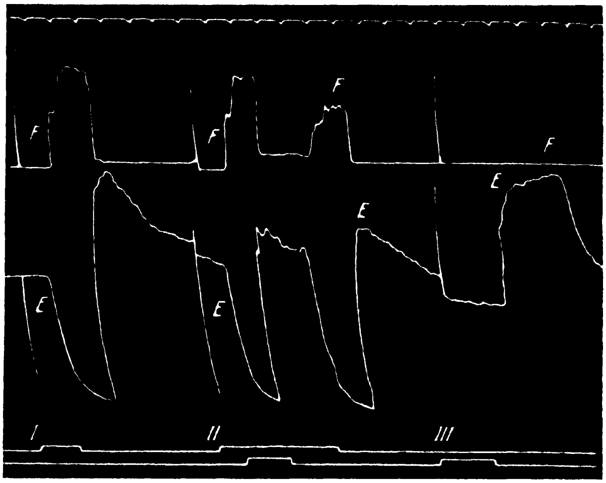


Fig. 232. Reciprocal innervation of antagonistic muscles: flexor of left side (m. semitendinosus) whose record of contractions is designated by *F* and extensor of left side (m. vastus cruralis) designated by *E*.

Vertical lines show mutual disposition of myograph levers. Rise of line, second from bottom, shows onset of stimulation of the distal end of left peroneal nerve. This stimulation *(I)* produces flexor reflex contraction of flexor and simultaneous relaxation of extensor. Sechenov's effect appears after discontinuance of stimulation: extensor which was inhibited during flexor reflex is greatly contracted. Second experiment *(II)* begins with stimulation of same left peroneal nerve simultaneously supplemented by stimulation of right peroneal nerve (rise of lower line). Flexion is inhibited, though not completely, and extension begins, being less pronounced than in experiment *III* where stimulation of right peroneal nerve produces only extension (after Sherrington).

in the motoneurons which innervate this muscle. When the efferent neurons of the extensors are inhibited, the tone of these muscles decreases or disappears and the muscle relaxes (Figs. 232 and 233).

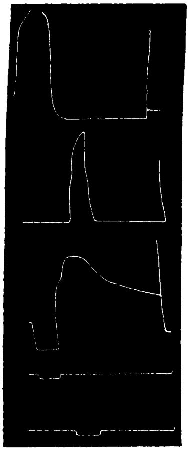


Fig. 233. Record of contractions (top to bottom) of right extensor, right flexor and left extensor of the leg of the cat.

Stimulation of sensory nerve of left foot (drop of line, second from bottom) produces contraction of extensor of right leg and relaxation of extensor of left leg; subsequent stimulation of sensory nerve of right foot (drop of bottom line) produces contraction of extensor of left leg and relaxation of extensor of right leg (after I. Beritov).

This type of inhibition is manifest in every reflex act. During the expiratory movement inspiration is inhibited, the tone of the intercostal muscles and the diaphragm decreases. When the eye is turned to the outside the muscle which turns the eyeball inside relaxes (this case of reciprocal inhibition already attracted the attention of Descartes). Under reflex excitation of the vagus the antagonistic sympathetic innervation of the heart is inhibited. *Normally every reflex act inhibits all activities unrelated to it.* Consequently, any normally proceeding reflex not only consists of excitation spreading along a definite reflex arc, but necessarily also includes the process of inhibition arising in other reflex arcs.

The inhibition of reflexes which *at the given moment and under the given conditions* are antagonistic to the reflex that is being accomplished is often designated as reciprocal inhibition. It is a very important factor in the coordination of reflex activity, since without inhibition which reciprocally arises in each reflex act the responses would be generalized. Impaired or inadequately elaborated reciprocal inhibition results in greater or lesser generalization of the reflexes which diminishes the effectiveness of the reflex acts. Such impairment of reciprocal inhibition manifests itself, for example, during the development of fatigue which interferes with coordinated movements (everybody knows the expression "to stagger with fatigue").

The phenomena of reciprocal inhibition have been studied mainly with regard to motor reflexes, but they are also important in the reflex regulation of the work of internal organs. Stimulation of the interoceptors of the blood vessels and internal organs modifies the reflex activity of the skeletal muscles (Fig. 234). The motor reflexes in their turn influence the reflex regulation of the internal organs.

The distribution of excitation and inhibition in various neurons depends on the activity of the higher divisions of the central nervous system, which establishes different correlations and connections between the neurons of the lower nervous centres.

Elaboration of Reciprocal Inhibition and Coordination of Reflex Activity

Formation of antagonistic relations between reflexes. The division of various effectors and, consequently, various reflexes, into antagonistic and synergetic (i.e., reinforcing one another) is by no means invariable; synergetic and antagonistic relations between effectors are formed in the process of reflex activity and depend on the traits of the organism peculiar both to the species and individuals.

For example, the flexors and extensors of an extremity function as antagonists only at a definite stage of flexion and extension. During rapid flexion of the extremities as, for example, in running the extensors begin to contract towards the end of the contraction of the flexors, thus ensuring a rapid transition to the next phase of movement. During an alimentary reflex act the salivary gland is reflexly stimulated simultaneously with the contraction of the masticatory muscles and the muscles of the larynx which contract during deglutition. In the vomiting reflex the salivary gland is also reflexly stimulated, but the masticatory muscles, the muscles of the larynx, oesophagus and cardial sphincter relax, their contraction being inhibited.

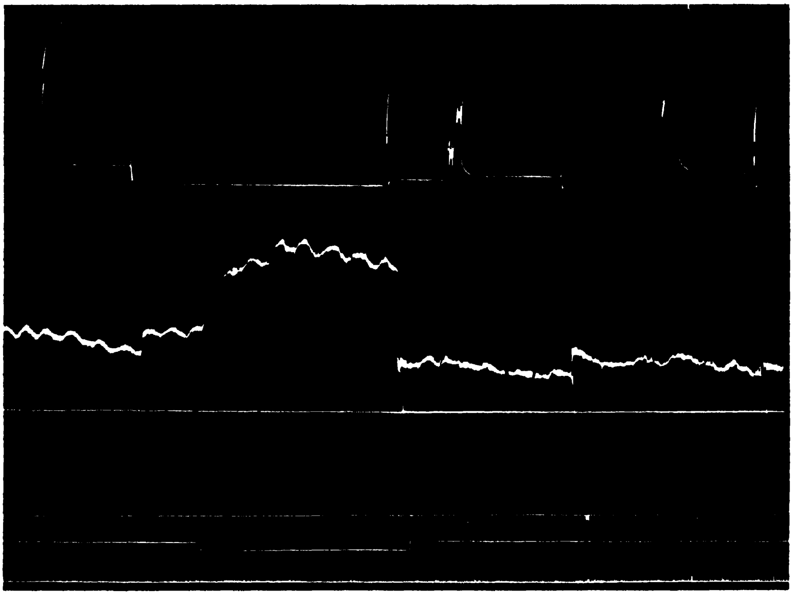


Fig. 234. Inhibition of motor reflexes in the cat under increased pressure in urinary bladder.

Top curve: record of contractions of erect muscle of the thigh produced reflexly by stimulation of afferent nerve fibres (this stimulation is marked on third line from bottom). Second line from bottom registers pressure increase in urinary bladder. This stimulation produces reflex increase in blood pressure (second line from top) and inhibition of motor response. Bottom - time interval (in seconds) (after O. Merkulova and V. Chernigovsky).

Isochronism of simultaneously functioning efferent neurons and effectors. The motoneurons and muscles whose excitation is simultaneous in the reflex acts that are of prime importance for each species have similar lability (p. 496) and a similar chronaxie (p. 495). In such movements .as walking, which is important for the majority of animals, the flexors of each extremity during the phase of its flexion contract more or less simultaneously; the extensors during the greater part of this period also simultaneously relax (during the phase of extension these relations are inverse). The study of the chronaxie of muscles and nerves in human beings and animals revealed that the muscles functioning as antagonists in the most constantly repeated movements have different chronaxies (Bourguignon, Ufland and others). Thus, in adults the chronaxie of the flexors of the leg (*m. semitendinosus*) is 0.50 to 0.60 m/sec., and that of its extensors (*m. quad-*

riceps) 0.13 to 0.15 m/sec.; the chronaxie of the flexors of the wrist and fingers is 0.20 to 0.36 m/sec. and that of their extensors 0.44 to 0.72 m/sec. With a readjustment of the functional role of the muscles these relations radically change.

Readjustment of the coordination of reflex acts involving the higher divisions of the nervous system. The fact that excitation and inhibition are distributed through definite efferent neurons in the process of the functioning of the central nervous system was most strikingly demonstrated by experimentally induced changes in the innervation and function of various effectors.

If the distal part of one severed nerve is sutured to the peripheral part of another nerve, the effector, to which the axons still connected with their cell body will grow, will receive impulses from neurons which usually innervate entirely different effectors. Afferent fibres growing in along the degenerate fibres will similarly become connected with other rather than normal receptors. It has been found that under such an experimental readjustment of the connections of afferent and efferent neurons the normal activity of organs with a completely reshaped innervation recovers in a certain (sometimes long) period of time (Flourens, Weiss, Bethe, Anokhin et al.). For example, after anastomosing the distal portion of the vagus with the peripheral portion of *n. cutaneous brachii* kneading and stretching the skin at first provokes vomiting as if the receptors of the stomach and the intestinal tract, from which some of the afferent fibres of the vagus previously extended, were stimulated. Some time later, kneading the skin on the paw no longer provokes vomiting; pricking the foreleg causes the animal to jerk the paw away; in running and walking the extremity, innervated by neurons which previously innervated the stomach or the heart, contracts normally in coordination with the movements of the extremity that has retained its usual innervation (P. Anokhin).

It has furthermore been shown (Flourens, Bethe, E. Asratyan, and others) that an animal can move normally even when the articulations of the muscles are changed, for example, by suturing the tendon of the flexor of the leg, i.e., *m. semimembranosus*, to the place where the extensor muscle, i.e., *m. quadriceps,* is attached, and by suturing the tendons of the latter to the remaining part of the severed tendon of *m. semimembranosus*. To flex the leg it is *m. quadriceps* which must now contract instead of *m. semimembranosus*; contrariwise, *m. semimembranosus,* which normally functions as a flexor, must contract to extend the leg. Consequently, some time after changing the articulation of the muscles new coordinative relations are elaborated. The muscles with the rearticulated tendons again become antagonists; but now the flexor relaxes where it formerly contracted and contracts where it normally relaxed. The chronaxie of the muscle, a flexor by nature, but functionally converted into an extensor, becomes the same as that of the extensor (Y. Ufland).

Investigations carried out by E. Asratyan have established the fact that the *reorganization of the coordinative relations depends on the activity of the higher part of the brain.* After a radical readjustment of the connections between the efferent neurons and effectors (experiments with stitching together certain nerves), after the creation of new pathways along which impulses are propagated in the centres (splitting the spinal cord), after the modification of the functional significance of the effectors (rearticulation of tendons), the functions are not recovered, and the recovery already achieved disappears if the cerebral cortex is removed. This leads to the conclusion that the activity of the division of the central nervous system, which is the highest in the given class of animals, is responsible for the formation of coordinative relations during its phylogenetic development.

Emergence of Inhibition Under Action of Strong Stimuli

The action of strong stimuli on the centres is an important factor in determining the emergence of inhibition (Fig. 235).

I. Sechenov found that strong stimulation of the skin or afferent nerves of a spinal (or decerebrate) frog produced either no reflex contraction of the skeletal muscles at all or a very weak contraction. Immediately upon discontinuance of stimulation a strong reflex contraction of the muscles occurred. This muscular contraction following the suspension of stimulation which has reflexly produced inhibition is due to succession of inhibition by excitation and is designated as Sechenov's effect. The decerebrate frog, for example, is almost motionless when its skin is subjected to strong and frequent induction shocks, but jumps as soon as the current is switched off. This means that strong stimulation of the centres (in this experiment the centres of the spinal cord) inhibits their excitation. The effect of excitation manifests itself in the traces of this stimulation.

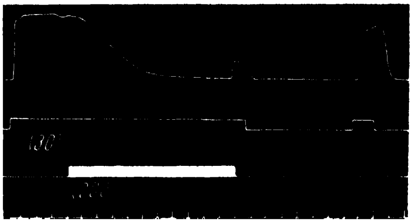


Fig. 235. Inhibition of reflexes under action of frequent stimulations of afferent fibres.

Top to bottom: [illegible] of contraction of m. semitendinosus [illegible] decerebrate cat; stimulation of peroneal nerve on same side at relatively low frequency (30 per second); stimulation of same nerve trunk at high frequency (200 per second). Figure shows that frequent stimulation inhibits response. Sechenov's effect appears after discontinuance of frequent stimulation (data obtained by laboratory headed [illegible] Y. Volborth).

Strong stimulation produces inhibition in all structures of the central nervous system, but the intensity of stimulation which produces it varies. The most pronounced inhibitory action of supramaximal stimuli is revealed by studies of the activity of the cerebral cortex.

Interrelations Between Excitation and Inhibition. Hysteriosis

Conversion of inhibition into excitation. Inhibition always develops in connection with the process of excitation, either arising in one group of neurons when another group is excited, or as a reaction of the nervous structures to strong, frequent (or long-repeated) impulses of excitation. But inhibition may, in its turn, lead to excitation or heightened excitability. This is most clearly manifested in the activity of the cerebral cortex, though it is also evident in the spinal cord separated from the higher centres.

Hysteriosis is a heightened excitability of the central nervous system resulting from a protracted flow to the centres of impulses produced by continued intermittent stimulation of the afferent fibres of some nerve. Such stimulation very soon ceases to produce a response, since inhibition (and possibly fatigue as well) develops in some link of the reflex arc. But continued stimulation of the afferent fibres produces a gradual rise in the excitability of other reflex arcs usually within 100 to 200 minutes. This manifests itself in the fact that reflexes from other afferent nerves are then produced by weaker stimulation than in the absence of protracted tetanization of some afferent nerve.

The phenomenon of hysteriosis was also very clearly discovered in mammals under a protracted (60 to 180 minutes) tetanization of afferent fibres from the receptors of the skin and the abdominal viscera.

Phenomena of Simultaneous and Successive Induction

We have seen that in the course of some reflexes, while a certain group of central neurons becomes excited, a state of inhibition or lowered excitability arises in other neurons of the central nervous system; contrariwise, when a group of neurons becomes inhibited, a state of excitation or heightened excitability may arise in other neurons of the central nervous system. Consequently, the process of excitation in some nervous structures engenders, as it were, a state of inhibition in other, more or less remote nerve cells. Similarly, the process of inhibition developing in certain nerve cells engenders a process of excitation (or heightened excitability) in other nerve cells.

In physics generation of an electric current flowing in an opposite direction in a remote conductor is called induction. By external analogy the term "induction" was applied by Sherrington to the emergence in the nerve cells of a process opposite to that which occurs in the "neighbouring neurons" (or previously occurred in the same neurons). If inhibition emerges around excited cells *while* they are still in a state of excitation, or if excitation (or heightened excitability) arises "in the neighbourhood" of inhibited cells *while* they are still in a state of inhibition, this group of phenomena is designated as *simultaneous* induction.

In induction we always deal with contrasting relations: one process "induces" the opposite process in the neurons which are not embraced by the first process. If excitation results in an inhibitory process, the induction is called *negative*, but if the contrasting relations lead to the emergence of excitation (or heightened excitability), the induction is called *positive* (Pavlov).

In addition, there are contrasting relations which develop in time within the same group of nerve cells and manifest themselves in an interchange of inhibition and excitation within these cells. This is the so-called *successive* induction.

In successive induction a state of lowered excitability arises in the nervous structures upon discontinuance of excitation in them, while in the inhibited neurons discontinuance of inhibition results in a state of heightened excitability which may manifest itself in excitation. Thus, successive induction implies either the passage of the excited centre to a state of inhibition after discontinuance of excitation (negative phase of successive induction), or the emergence of excitation in the inhibited centre after discontinuance of inhibition (positive phase of successive induction). Owing to these relations, disappearance of excitation predisposes the centre to development of inhibition; contrariwise, disappearance of inhibition predisposes the centre to development of excitation.

Phenomena of induction are particularly pronounced in the activity of the cerebral cortex (Chapter 62), but are also found in the lower divisions of the central nervous system. For example, observations of decerebrate animals show that an extensor inhibited (relaxed) in the course of the flexor reflex contracts after discontinuance of flexion (Fig. 232).

The relations between simultaneous and successive induction for the centres of antagonistic muscles can be illustrated by the following scheme:

State of Flexor and Extensor Centres During and After Flexor and Extensor Reflexes

Reflex phase:	Flexor centre:	Extensor centre:
During flexor reflex	Excited	Inhibited (simultaneous negative induction)
After flexor reflex	Inhibited (successive negative induction)	Excited (successive positive induction)
During extensor reflex	Inhibited (simultaneous negative induction)	Excited
After extensor reflex	Excited (successive positive induction)	Inhibited (successive negative induction)

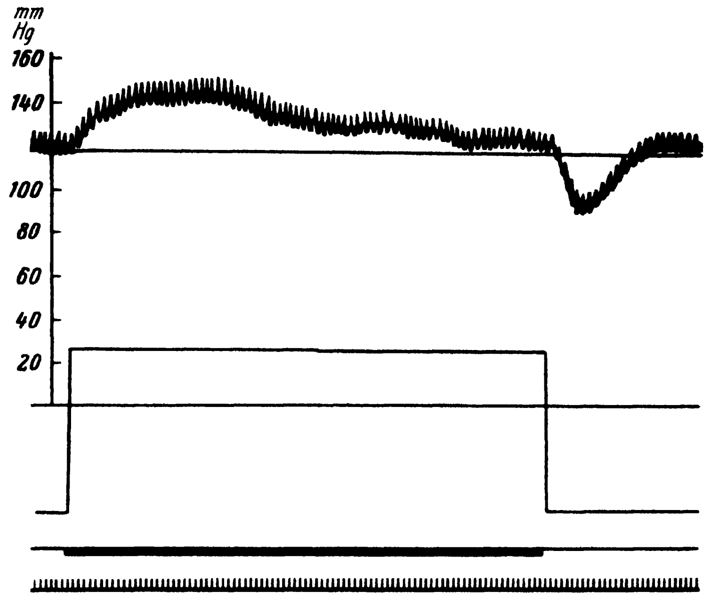


Fig. 236. Negative phase of successive induction (inhibition following excitation) in vasomotor centre. Discontinuance of stimulation of mechanoreceptors in intestinal tract, which produced excitation in vasomotor centre, leads to its inhibition reflected in drop of arterial pressure following its increase.

Top to bottom: record of blood pressure with its zero line, record of pressure in balloon which distends the loop of small intestine, mark of this stimulation and time interval (5 seconds) (after V. Chernigovsky).

The change of excitation to inhibition manifests itself clearly after reflex stimulation of the vasomotor centre (Fig. 236). The positive phase of successive induction conditions Sechenov's effect described on page 549.

Role of Impulses from Receptors in Coordination of Reflex Activity

When the activity of a certain organ changes in some way or other during a reflex the conditions of stimulation of its receptors invariably also change. Intensification of the activity of each organ generally also intensifies the generation of impulses from its receptors; transition of the organ to a resting state or a weakening of its activity are likewise perceived by the receptor apparatuses at least as a decrease in their stimulation.

The great significance of impulses, which arise in the receptors of effector organs, for the coordination of the reflex acts of these organs was first discovered by Sechenov who, as before stated, also discovered the phenomenon of central inhibition, the phenomenon subsequently termed "rebound" (Sechenov's effect), and the summation of excitation in the nervous centres. Sechenov found that if the extremity of the spinal frog is flexed, stimulation of the skin on the extremity causes it to extend, but if the extremity is extended, the same stimulation results in its flexion. This is due to the fact that impulses arising in the receptors of extensor muscles stretched during the extension of the leg increase the excitability of the neurons in the reflex arc of the flexor reflex, while impulses from the receptors of flexor muscles increase the excitability of the reflex arc of the extensor reflex.

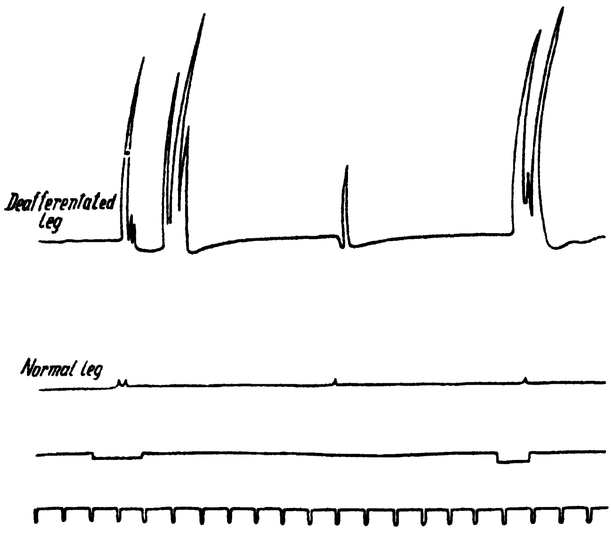


Fig. 237. Intensification of reflex contractions of extremity deprived of afferent innervation (deafferentated). Reflex contractions of muscles produced by stimulation of rectal receptors by inflation of balloon inserted into rectum.

Top to bottom: record of movements of deafferentated extremity; record of movements of extremity with normal innervation; record of stimulation of rectum; time interval (5 seconds) (after V. Chernigovsky and O. Merkulova).

Impulses from interoceptors act upon the central nervous system as soon as any reflex begins; the influence of these impulses on the central nervous system is always added to the influence of the stimulus provoking the given reflex. For example, the receptors of the salivary glands become excited during reflex salivation; stimulation of the receptors of the aortic arch and of the carotid sinus is modified by the reflex changes in cardiac activity, blood pressure, etc.

Thus each reflex act is a *chain reflex,* since the activity of the effectors itself stimulates the receptors situated in these effectors, and this, in its turn, leads to reflex responses of the central nervous system. Reflex responses produced by stimulation of the receptors, which are themselves stimulated by a previously originated reflex, unite with the latter into a single reflex act.

The role of impulses from muscular receptors in the coordination of motor acts is proved by the extreme awkwardness of movements following a section of the posterior roots or lesions of the afferent neurons of the spinal cord ("sensory ataxia"). A section of all posterior roots of the lumbar segments of the spinal cord on one side of the body produces continuous rhythmic contractions in the deafferentated extremity keeping time with the respiratory movements (L. Orbeli and K. Kunstman). Only when impulses from the receptors of the extremity no longer come to the spinal cord is there no more inhibition, which normally blocks the outlet for impulses irradiating with each inspiratory movement from the respiratory centre to the neurons of the lumbar divisions of the cord (an example of such intensification of reflexes on a deafferentated leg is shown in Fig. 237).

It has been found in the laboratory headed by K. Bykov that reflex salivation is essentially modified when the impulses from the receptors of the salivary glands are excluded.

Theory of Inhibition

The inhibitory process always arises in connection with the excitatory process and is inseparable from excitation. Such was the point of view of Pavlov and Wedensky; it has been also accepted by most foreign researchers working on this problem (and often proceeding from the investigations of Wedensky). The theory of inhibition, establishing its dependence on chemical, physicochemical and physical processes in the nervous tissue, can be developed only on the basis of precise facts relating to the nature of the processes of nervous excitation. But we have no such facts as yet.

The most substantiated theory of inhibition is Wedensky's theory of parabiosis, regarding inhibition as a modification of the excitatory process under which the latter turns into a stagnant, nonspreading process. This viewpoint interprets the emergence of inhibition as a result of conflicting excitatory processes, as the consequence of excitation increasing to the point where it loses its inherent indulant character.

The theory of parabiosis is of great methodological significance, since it regards the emergence of antipodal states as a result of quantitative development and modification of the most common property of living systems, i.e., their reaction to stimulation. This theory rejects the contraposition of the states of rest, excitation and inhibition to each other; it establishes transitional phases between them in the form of different levels of basal metabolism with corresponding different levels of excitability. Subthreshold stimulation of different strength provokes local excitation of different intensity in the nervous tissue; this excitation turns into a process, which spreads over the entire neuron and is also of graduated intensity; but when the intensity of excitation goes beyond a certain point, the excitation becomes stagnant and then ceases to be propagated. At this time the nervous tissue, especially the sections with low lability, falls into a state of parabiosis, which is characterized by all the symptoms of inhibition.

From the point of view of parabiosis the development of inhibition in the nervous centres is due to the fact that upon reaching a certain level excitation loses its oscillatory, impulsive character and turns into a stationary wave. This stable, nonfluctuating excitation Wedensky named parabiosis. The cells affected by it do not propagate or conduct impulses of excitation, i.e., exhibit all symptoms of inhibition.

Consequently, the emergence of inhibition under the action of impulses from afferent fibres on the centres does not depend on the properties of special "inhibitory" centres and "inhibitory" nerve fibres, as it is assumed by many researchers with Sherrington at the head. It depends, on the one hand, on the strength and frequency of the nervous impulses, and, on the other hand, on the properties of the nervous structures which react to them at the given moment. These properties of the nervous structures reacting to stimulation are determined both by the preceding activity and by the response to the acting impulses. When the lability of the centre is high and the aftereffect of each impulse is transitory, the summation of impulses and the transition of the centre to inhibition are impeded; on the contrary, low lability contributes to the development of inhibition.

From the point of view of Wedensky's theory it is clear that stimulation reaching the centres from the same afferent fibres may either increase the excitation of the given centre or inhibit it. If weak or infrequent impulses meet in a certain group of neurons, or if impulses of excitation come to a centre which is already in a state of weak excitation, they intensify the effects of excitation. This is a case which characterizes the phenomena of facilitation and dominant. But when strong (or frequent) impulses meet in certain neurons, or when impulses arrive at a centre already considerably excited, inhibition results and the effect of excitation of this centre abruptly disappears.

Parabiotic phases in the development of central inhibition. An essential argument in favour of Wedensky's theory is the emergence of so-called parabiotic (or hypnotic) phases in the process of development of inhibition; these phases coincide with the phases (also described by Wedensky) which arise during development of nonconductivity in the nerve fibre. Characteristic among them is the paradoxical phase. In this phase the reflex reaction to strong (or frequent) impulses is weaker than to weak (or infrequent) impulses.

In the lower nervous centres the paradoxical phase can be detected much easier by varying the frequency of stimulation that its intensity. In the latter case, excitation involves new neurons, and a more intense stimulation of the afferent nerves often "breaks down," as it were, the phenomena of inhibition. But by varying the frequency of the induction shocks applied to the afferent fibres one can easily observe that more frequent stimulation results in a weakening or disappearance of the reflex reactions of the centre, which becomes completely inhibited, whereas infrequent stimulation produces strong reflex responses.

The parabiotic phase is particularly pronounced when inhibition develops in the cerebral cortex (Chapter 60).

. Inhibition cannot be regarded as a state which is identical to fatigue: while the former often arises very rapidly (within several thousandths of a second), the latter develops only in the course of prolonged activity; whereas the former is an indispensable condition for the normal activity of the centres, the latter characterizes a certain derangement of their normal activity. At the same time there are reasons to believe that in a number of cases inhibition arises under the same conditions that may lead to the development of fatigue. The emergence of inhibition may prevent the development of a serious disturbance in the normal metabolism of the nerve cells, which is sometimes designated as exhaustion, and apparently arises during the development of considerable fatigue.

B. PROPERTIES AND ACTIVITY OF THE LOWER DIVISIONS OF THE CENTRAL NERVOUS SYSTEM (UP TO AND INCLUDING SUBCORTICAL GANGLIA) VEGETATIVE NERVOUS SYSTEM

CHAPTER 55

CONNECTIONS OF NERVOUS CENTRES WITH RECEPTORS AND EFFECTORS

Afferent fibres extending from all receptors (except the olfactory and visual) enter the spinal cord and the medulla oblongata which are the phylogenetically oldest structures of the central nervous system. These structures contain cell bodies of efferent neurons innervating all the organs of the body (only the nerve cells which by their axons innervate certain muscles of the eye, lie above the medulla oblongata—in the midbrain). In the spinal cord and medulla oblongata there is a mass of internuncial neurons involved in the coordination of reflex acts.

Magendie's Law and Metamerism of the Spinal Cord

Magendie's law. All afferent fibres enter the spinal cord through the posterior roots and the efferent fibres issue from it through the anterior roots. This is the so-called Magendie's law (sometimes called the Bell-Magendie law); with its discovery the nerve fibres were, for the first time, divided into afferent and efferent fibres, which played an important role in the development of the reflex theory. Magendie (in 1823) discovered this law and showed that stimulation of the central part of any posterior spinal root provoked a very strong pain reaction, whereas stimulation of its peripheral part provoked no movements at all. Contrariwise, stimulation of the central part of any anterior root produced no effect, while stimulation of its peripheral part always resulted in contraction of definite muscles. Section of the posterior roots paralyzed sensibility, while section of the anterior roots paralyzed the musculature.

A seeming exception from Magendie's law is the pain reaction observed during stimulation of the central part of the anterior roots, if the posterior roots are not severed. This pain reaction is accounted for by the fact that from the point of junction of the anterior and posterior roots afferent fibres of the posterior root, connected with the receptors of the meninges, enter the anterior root. This so-called recurrent sensibility of the anterior roots disappears after section of the respective posterior root (*Cl. Bernard*).

The following experiment illustrates the role of the anterior and posterior roots. If we sever the posterior roots of the lumbar and sacral segments on the right side (this can be done easiest in the frog) and then sever the corresponding anterior roots on the left side, the entire right leg will lose its sensibility, though it will fully preserve the ability to move; contrariwise, the left leg will retain sensibility, but its muscles will be totally paralyzed. A pinch of the right leg, therefore, does not provoke any movements of the animal, but the same leg moves when the left leg, which has retained its sensibility, is stimulated (experiment of J. Müller, 1832).

Magendie's law has also been demonstrated by histological methods. It is a well-known fact that after an axon is sectioned, its part separated from the cell body degenerates. If the posterior roots are cut at the periphery of the spinal ganglion, all (afferent) fibres which extended from this ganglion to the receptors degenerate; if the posterior root is cut between the ganglion and the cord, all the nerve fibres which issued from the given root and extended along the ascending pathways of the spinal cord degenerate. Finally, when the anterior root is severed, all the motor nerve fibres degenerate.

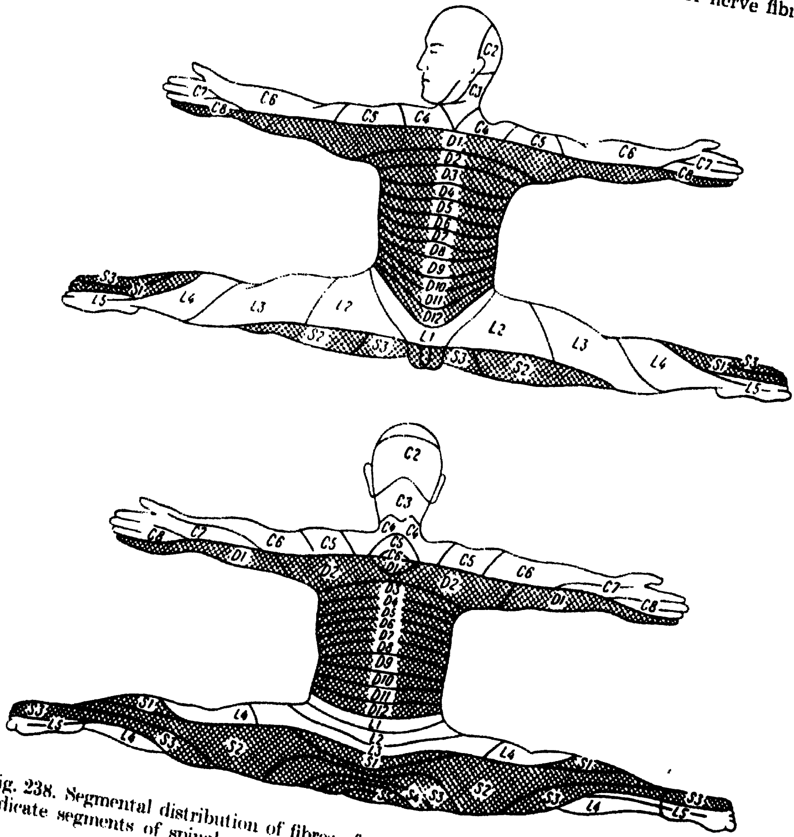


Fig. 238. Segmental distribution of fibres of posterior roots in skin. Letters and figures indicate segments of spinal cord which, in the main, project afferent fibres to given cutaneous area.

Metamerism of root innervation. Each pair of spinal roots (and each cranial nerve) innervates a definite area of the skin and definite skeletal muscles.

The segments of the spinal cord and their roots are designated by letters; the letters indicate the intervertebral apertures through which the roots corresponding to these or other vertebrae issue; each vertebra corresponds to one segment of the body, or, as it is often called, one *metamere*. The cervical vertebrae are marked with the letter "C," the thoracic with "Th" or "D" (Dorsal), the lumbar with "L," and the sacral with "S."

The roots of the sacral and lumbar segments of the spinal cord innervate the skin and muscles of the perineum (S_4-S_5), lower extremities (L_2-L_5 and S_1-S_3) and lower part of the trunk. The roots of the thoracic segments innervate the skin, blood vessels and muscles of the trunk and upper extremities (D_1 and D_2). The roots of the cervical segments innervate the skin and muscles of the upper extremities and shoulders (C_4-C_7) of the neck, occiput and diaphragm (C_3-C_5). The muscles and skin of the face are innervated by cranial nerves (trigeminal and facial).

The distribution of the fibres of each pair of roots among definite parts of the body is connected with the segmental structure of the spinal cord. The segmental structure of the body is strongly pronounced in a number of invertebrates (worms and insects), each segment usually containing a pair of ganglia. In vertebrates there is no such segmental structure of the body, but in the embryonic period the higher animals go through the phase of segmental structure; the muscles which begin to develop then in each segment are called myotomes, and the part of the skin surface relating to each segment is called a dermatome. In the skeleton, especially in the spinal column, of an adult there are traces of this segmental structure.

Fig. 238 shows with which roots the receptors of this or other area of the skin are connected. It will be observed that the nerve fibres of each pair of the posterior roots extend to the receptors not only of their "own" metamere, but also of each metamere situated above and below it. For example, in order fully to desensitize the area shown in Fig. 238 as corresponding to posterior roots D_8, it is necessary to cut not only the eighth, but also the seventh and ninth thoracic posterior roots. The same is observed in the innervation of the muscles: each of them is innervated by two or three anterior roots.

These facts are of great importance for diagnosing lesions in the spinal cord and peripheral nerves. They make it possible to establish precisely which sensory (or motor) paralyses are caused by lesions of these or other segments of the spinal cord and the roots connected with them. A nerve trunk usually contains nerve fibres from several spinal segments, and the loss of sensibility resulting from any lesion of the nerves therefore differs from that produced by lesions of the posterior roots.

Connections of Medulla Oblongata with Receptors and Effectors

Afferent fibres from the receptors of the organ of hearing, labyrinth, oral cavity, skin of the face, organs of the thoracic cavity (heart, large blood vessels and lungs) and from the receptors of a number of abdominal organs (stomach, pancreas, liver, bile ducts, small intestine) enter the medulla oblongata. Some receptors of the thoracic and abdominal cavities are also connected with the spinal cord.

Efferent fibres from the neurons of the medulla oblongata innervate all the muscles and glands of the face, heart, bronchi, larynx, oesophagus, stomach, pancreas, liver and intestinal tract. The innervation of internal organs by parasympathetic fibres from the medulla oblongata is coordinated with the innervation of the same organs by sympathetic fibres from the nerve cells lying in the spinal cord.

The medulla oblongata is connected with the receptors and effectors by fibres of the *cranial* nerves. Whereas the functions of each pair of the posterior and anterior spinal roots can be largely replaced by the functions of the lower or higher pair of roots because of the overlapping of the spinal metameres, each cranial nerve performs functions peculiar to it alone.

Like all nerve fibres, those of the cranial nerves (of which I-V are not directly connected with the medulla oblongata) are divided into afferent and efferent fibres. The afferent fibres of these nerves are subdivided into: a) afferent fibres extending from the specialized receptors of the head, such as the receptors of the organs of smell (fibres of the first pair of cranial nerves), vision (second pair), hearing, labyrinth and taste (eighth pair); b) afferent fibres extending from the receptors of the skin (in the fifth pair of cranial nerves) and muscles of the face (mainly, in the seventh pair), and c) afferent fibres from the interoceptors of the vascular, alimentary and respiratory systems which run, mainly, in the trunk of the vagi (the tenth pair and also in the ninth pair of cranial nerves).

The trunks of the cranial nerves (except the I, II and VIII pairs) are mixed nerves containing both afferent and efferent nerve fibres. But in the centres the cells which give off fibres of different kinds form separate groups designated as *nuclei* of the corresponding nerves.

CHAPTER 56

VEGETATIVE NERVOUS SYSTEM

Characteristics of the Vegetative Nervous System as a System of Efferent Neurons

The vegetative nervous system includes all the efferent neurons except the motoneurons.

All efferent neurons—vegetative as well as motor—are none other than terminal links of diverse reflex arcs. These neurons only convey to the effectors the impulses by which the nervous centres respond to stimulation of the receptors, i.e., reflexly. The conceptions which ascribe autonomy to the vegetative nervous system and thus oppose the regulation of the activity of the internal organs to the regulation of the behaviour of the organism in its environment are erroneous.

The idea of the autonomy of the vegetative nervous system was advanced at the end of the 18th century by Bichat, talented French physician and naturalist, who believed that the organism included organs of "vegetative" life (organs of blood circulation, digestion, excretion, metabolic processes) and organs of "animal" life (the central nervous system, the sense organs and the skeletal muscles). Bichat thought all processes of vegetative life to be influenced by the ganglia of the sympathetic nervous system, whereas all phenomena of animal life, characterized by the movements of the animal, were controlled by the cerebrospinal system under the action of impulses coming from the sense organs.

Between 1890 and 1920, Gaskell and Langley, British researchers, thoroughly studied the structure of the vegetative nervous system which Langley termed the "autonomic" nervous system. This denomination may create the impression that the system functions as an allegedly independent formation according to its own specific laws and in this way controls the activity of the internal organs and the blood circulation. Discovery of the influence exerted by stimulation of the hypothalamus on a number of internal organs gave rise to the question of special centres of the vegetative nervous system. Many clinicians began to interpret some pathological states as a result of changes *initially* arising either in the sympathetic division, or in the parasympathetic division of the vegetative nervous system. L. Orbeli and his co-workers discovered some previously unknown aspects of the activity of the sympathetic nervous system, however, and considered the influences exerted through the vegetative nervous system apart from the normal reflex activity of the organism as a whole.

Actually there is no autonomic activity of the vegetative nervous system because this system never functions separately and independently of other nervous structures, including the cerebral cortex. Nor are there any independent vegetative reflexes. Impulses to the effectors are transmitted along the vegetative system only when they arise in the nerve centres in response to stimulation of the receptors, and the reflex activity of the centres involving the cerebral cortex is never confined to the conveyance of impulses *only* to the vegetative neurons.

Structure of the Sympathetic and Parasympathetic Divisions of the Vegetative Nervous System

Because of the specific structural features of the vegetative nervous system (see p. 38 and Fig. 2), excitation reflexly arising in the centres and conducted to the effectors from the nervous centres along the vegetative nervous system must invariably pass at least through two neurons (Figs. 2 and 239), namely: a) the first neuron whose cell body lies in the central nervous system and whose axon reaches the ganglion and forms the preganglionic nerve fibre and b) the second neuron whose cell body lies in the ganglion and whose axon forms the postganglionic fibre and is directly connected with the effector it innervates.

Location in the central nervous system of nerve cells whose axons form preganglionic fibres of the vegetative nervous system. The nerve cells which give rise to preganglionic fibres of the vegetative nervous system lie in very definite regions of the brain and the spinal cord and thus determine the following structure of the vegetative system (see Fig. 2):

1. *The cranial division* which includes: a) the mesencephalic region formed by neurons whose cell bodies lie in the so-called Yakubovich's nucleus in the midbrain and give off axons which enter the third pair of cranial nerves; b) the bulbar region formed by neurons whose cell bodies lie in the medulla oblongata and give off axons entering the seventh, ninth and tenth pairs of cranial nerves.
2. *The thoracolumbar division* formed by neurons whose cell bodies lie in the lateral columns of the gray matter of all thoracic segments and in two or three superior lumbar segments of the spinal cord.
3. *The sacral division* formed by neurons whose cell bodies lie in the second, third and fourth sacral segments of the spinal cord.

The cranio-bulbar and sacral divisions of the vegetative nervous system give rise to preganglionic fibres of the so-called *parasympathetic* system, while the thoracolumbar division forms preganglionic fibres of the *sympathetic* system.

Sympathetic and parasympathetic systems. The sympathetic system includes: a) all neurons whose axons form preganglionic sympathetic fibres extending to the sympathetic ganglia; the bodies of the nerve cells forming these preganglionic sympathetic fibres lie in twelve thoracic and two or three superior lumbar segments of the spinal cord; b) all sympathetic ganglia with their nerve cells at which preganglionic fibres from the thoracolumbar division terminate; c) all postganglionic fibres which issue from the cells of these ganglia. The *parasympathetic* system includes all neurons whose axons issue from the cranio-bulbar and sacral divisions of the vegetative system and all parasympathetic ganglia with their cells and postganglionic fibres extending from them.

All preganglionic fibres issuing from the thoracolumbar division of the spinal cord (i.e., all preganglionic sympathetic fibres) run to macroscopically visible sympathetic ganglia which form the sympathetic chain, and to the coeliac and mesenteric ganglia situated in the abdominal cavity. The postganglionic fibres which connect the ganglia of the sympathetic system with the effectors always run for some distance before reaching the organ they innervate. All preganglionic fibres issuing from the cranio-bulbar and sacral divisions (parasympathetic fibres) go to the parasympathetic ganglia, at whose cells they terminate. These parasympathetic ganglia are almost invariably aggregations of nerve cells scattered through the organs innervated by the postganglionic parasympathetic fibres which extend from the given ganglia. Such are, for example, the aggregations of nerve cells in the heart, known as Remak's, Dogiel's and other ganglia. The postganglionic fibres emerging from the cells of the ganglia of the parasympathetic system, which are situated in the organs innervated by this system, are short and their preparation is difficult (only those nerve cells at which the preganglionic parasympathetic fibres, running to the salivary glands, lachrymal glands and smooth muscles of the eye, terminate, lie outside the effectors [but also very close to them] in the *submaxillary* and *ciliary* ganglia).

Another difference between the parasympathetic and sympathetic systems is that in the former the interval between the emergence of nerve impulses in its fibres and the reactions of the effectors to these impulses is very short (several hundredths or thousandths of a second). The aftereffect observed in the effectors when stimulation of the parasympathetic system is discontinued is similarly short. But the effect of excitation transmitted along the neurons of the sympathetic system begins to manifest itself only a few seconds (sometimes almost one minute) after the emergence of nervous impulses in the sympathetic fibres. When the stimulation of the sympathetic fibres is discontinued, the effect of their excitation persists for many seconds, and sometimes even minutes.

The rate of conduction of nervous impulses in the parasympathetic fibres is usually also higher than in the postganglionic sympathetic fibres, some of which are unmyelinated.

Some substances exert a specific influence on certain sections of the vegetative system; this phenomenon is utilized for the elective exclusion or, on the contrary, excitation of this or other division of the vegetative system. ***Atropine*** paralyzes the transmission of impulses from the postganglionic parasympathetic fibres to the effectors (an injection of atropine discontinues the action of the vagus upon the heart, the fibres of the oculomotor nerve upon the pupil and the chorda tympani upon the salivary glands, owing to which the heart rate increases, the pupil dilates and the secretion of saliva ceases). ***Ergotamine*** paralyzes the transmission of impulses from the postganglionic sympathetic fibres to the effector (its administration, for example, discontinues the constriction of the blood vessels resulting from the excitation of the sympathetic fibres). ***Nicotine*** acts upon the ganglia electively; at the final stage of its action it paralyzes the transmission of impulses from preganglionic to postganglionic fibres. This poison acts upon the junction (synapse) of the preganglionic fibres and the cells lying in the ganglia both of the sympathetic and parasympathetic systems. ***Pilocarpine*** and ***muscarine*** excite the terminal apparatuses of the postganglionic parasympathetic fibres (the administration of pilocarpine lowers the heart rate and increases salivation).

Acetylcholine reproduces the action of almost all preganglionic fibres on the cells of the ganglia of the vegetative system and the excitatory effect of all postganglionic fibres of the parasympathetic system, while adrenalin reproduces almost all the effects of excitation of the sympathetic postganglionic fibres.

Tonic Excitation of Vegetative Nervous System

The neurons of the vegetative nervous system acting upon the heart, smooth muscles of the blood vessels and intestinal tract are in a state of continuous (though variable), protracted tonic excitation characterized by rhythmic, now more and now less frequent impulses. This tonic excitation of the neurons of the vegetative nervous system is a result of their reflex reaction to impulses coming to the central nervous system from the receptors.

Rhythmic outbursts of excitation arise in the cells of the sympathetic ganglia which give off accelerating and reinforcing fibres to the heart (and maybe in cells of other ganglia as well) a few days after section of the preganglionic fibres which run to them. The emergence of impulses of excitation in decentralized ganglia (i.e., ganglia disconnected from the central nervous system) may have something to do with the heightened sensibility to acetylcholine and adrenalin acquired by them (Cannon). A number of afferent fibres (axons of Dogiel's cells, type II) terminate in the ganglia forming synapses on the cell bodies of the ganglionic efferent neurons. Impulses from receptors transmitted along afferent fibres to the ganglion provoke the peripheral reflexes already described on p. 534. Against the background of heightened excitability of the decentralized ganglia the impulses that produce these peripheral reflexes may prove very effective.

Influence of Impulses Transmitted Along Sympathetic and Parasympathetic Nervous System

Preganglionic sympathetic fibres emerge from the spinal cord in the first to the twelfth thoracic and the first to the third lumbar anterior roots and run in a common trunk formed by the fibres of the anterior and posterior roots; then they group themselves into discrete branchings called *rami communicantes albi*, enter the sympathetic trunk and travel with the latter to some sympathetic ganglion or other (these *rami communicantes* are white because the preganglionic fibres usually have a myelin sheath). Some postganglionic fibres, which are processes of ganglionic cells, have no myelin sheath and their bundles are, therefore, grayish. Such fibres form the *rami communicantes grisei* which run from the ganglion to the nerve trunks (Fig. 239) and through which they reach the effector.

On entering the *sympathetic* trunk through *rami communicantes*, the preganglionic sympathetic fibre does not necessarily terminate at the cells of the nearest sympathetic ganglion. Some preganglionic fibres pass without interruption through the nearest and sometimes even through the second successive ganglion of the sympathetic chain and terminate at a cell residing in a remoter ganglion (Fig. 240).

Although preganglionic fibres do not emerge from the spinal cord below the second or third lumbar segment or above the inferior cervical segment there are still some cervical ganglia of the sympathetic system (from one to seven, but more often two or three) and sacral ganglia (four or five); consequently, the number of sympathetic ganglia exceeds the number of segments of the cord, whence the preganglionic sympathetic fibres originate. The large sympathetic ganglia of the abdominal cavity—the coeliac ganglion which the preganglionic fibres reach in the trunk of the splanchnic nerve and the superior and inferior mesenteric ganglia—also lie outside the sympathetic chain. The postganglionic fibres extending from the cells of these ganglia innervate the organs and blood vessels of the abdominal cavity and the small pelvis.

In each ganglion, where some sympathetic fibre terminates, the latter enters into connection not with one but with many nerve cells which give off postganglionic fibres.

Nicotine makes impossible the transmission of impulses from a preganglionic to a postganglionic fibre, but does not affect the conductivity of the vegetative fibres (when administered in small concentrations). By applying nicotine to the ganglia it is possible to find out precisely in which ganglion the particular fibres break off.

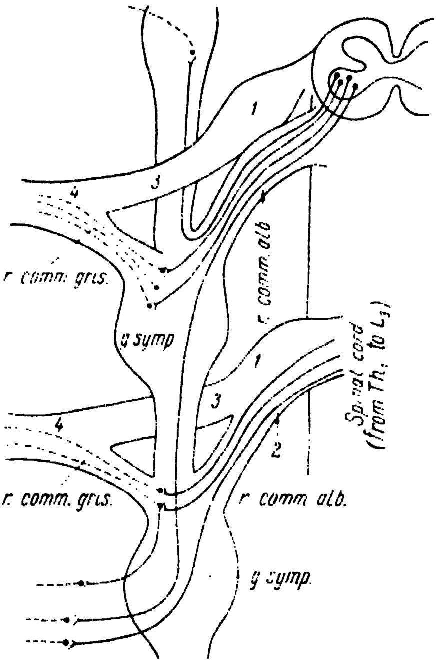


Fig. 239. Diagram illustrating emergence of sympathetic nerve fibres from spinal cord and their subsequent course.

1—gangl. spinale; *2*—anterior root; *3*—posterior root; *4*—mixed nerve; *g. symp.*—sympathetic ganglia. Postganglionic sympathetic fibres are indicated by dotted lines (after Fulton).

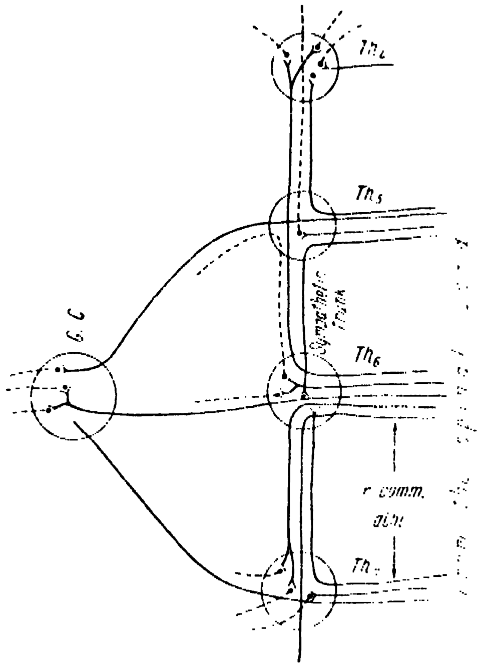


Fig. 240. Diagram illustrating the passage of preganglionic sympathetic nerve fibres (solid lines) through ganglia, and their terminals in one of the ganglia at cells giving off postganglionic fibres (dotted lines).

G. C.—gangl. coeliacum.

The influence of impulses transmitted along the neurons of the sympathetic nervous system on the glands, heart, blood vessels and smooth muscles has already been considered, and this is why only a general idea is given here.

Influence of impulses transmitted along neurons of sympathetic nervous system upon skeletal muscles. Studies in the laboratories headed by L. Orbeli showed that impulses transmitted along the fibres of the sympathetic nervous system may also influence the skeletal muscles. Experiments show that the efficiency of a fatigued muscle increases when fibres of the sympathetic nervous system are stimulated (Ginetsinsky's experiment). Fig. 241 shows that the intensity of muscular contractions of the fatigued muscle increases if the sympathetic nervous fibres are stimulated in addition to the motor fibres. Stimulation of sympathetic fibres cannot by itself produce

Sympathetic Innervation of Various Organs

Organ	Influence of excitation of sympathetic fibres	Points of emergence of preganglionic fibres	Points of emergence of postganglionic fibres
Pupil (or, to be exact, Müller's muscle)	Dilation of the pupil (owing to contraction of Müller's muscle)	Th_1 (sometimes also C_7)	Superior cervical ganglion
Lachrymal glands	Tear secretion (influence is not very strong)	Ditto	Ditto
Salivary glands	Scanty secretion of thick saliva (for *gl. parotis* only an increase in thick residue of saliva)	Ditto	Ditto
Heart	Increased, quickened and intensified heart rate	Th_1-Th_4	Gangl. stellatum
Stomach (fundic glands)	Scanty secretion	Th_5-Th_{10}	Gangl. coeliacum and (for lower division of intestinal tract) gangl. mesentericum superior and inferior
Smooth musculature of stomach and intestines, except ileocaecal sphincter	Inhibition of contractions and weakening of tone		
M. detrusor	Inhibition of contractions and weakening of tone	L_1-L_3	Gangl. mesentericum inferior
M. sphincter urethrae	Increase in tone	L_1-L_3	Ditto
Small arteries of skin	Constriction	For head and upper extremities Th_1-Th_2	Cervical ganglia
Small arteries of abdominal organs	Constriction	For vessels of trunk and abdominal cavity Th_2-Th_{12}	Thoracic ganglia and gangl. coeliacum
Small arteries of lungs and brain	Inconsiderable constriction	—	—
Small arteries of skeletal muscles	Uncertain effect	For vessels of lower extremities L_1-L_3	Lumbar and sacral ganglia
Coronary vessels	Apparently, dilation	Th_1-Th_2	Gangl. stellatum
Sweat glands	Secretion	—	—
Pilomotors	Contraction causing hair to rise	—	—

Note: Data relating to the points of emergence and points of interruption of the sympathetic fibres innervating the indicated functions are approximate, since there may be certain individual variations.

muscular contraction, but it modifies the state of the muscular tissue, increasing its susceptibility to impulses transmitted along the motor nerves, shortens the chronaxie which is prolonged when the muscle is fatigued and causes certain changes in its physicochemical properties. Impulses conducted along the sympathetic nerves, according to the data obtained by Nekrasov, act upon the myoneural synapses where excitation passes from the motor nerve to the fibres of the skeletal muscles; the properties of the muscular tissue itself probably undergo a secondary change.

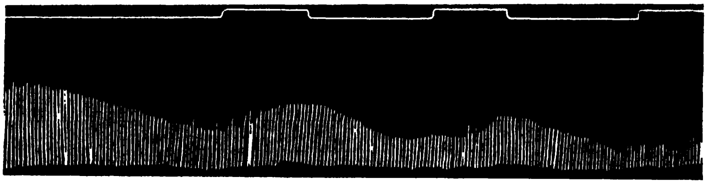


Fig. 241. Orbeli-Ginetsinsky phenomenon: intensification of contractions of fatigued muscle of the frog under stimulation of sympathetic nervous trunk (stimulation marked on upper line). Contractions of the muscle are produced by rhythmical stimulations of motor nerve fibres (after L. Orbeli).

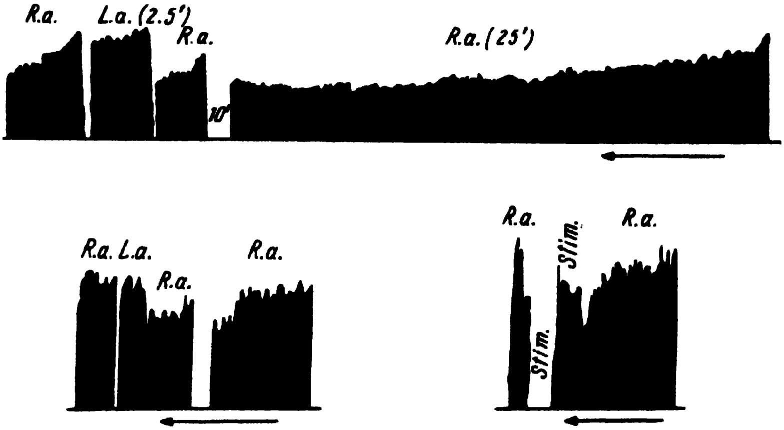


Fig. 242. Record of muscular contractions of arm lifting load in tact with metronome beats (weight load weighs 3 to 4 kilograms; 20 lifts per minute).

R. a. means right arm and *L. a.* - left arm.

Top (right to left): 25 minutes of work of right arm resulting in fatigue. After ten-minute rest right arm worked to point of fatigue less than first time. Then left arm worked 2½ minutes, owing to which right arm produced much more work subsequently.

Bottom, left: similar experiment performed on other person (first experiment was performed by Sechenov on himself). ***Bottom, right:*** influence of weak tetanization of skin of left arm (designated by "stim.") on efficiency of right arm (after Sechenov).

Excitation of the sympathetic nerve fibres acting upon the skeletal muscles (like any other influences of the sympathetic nervous system) manifests itself in effects similar to those which are caused by adrenalin (W. Cannon); adrenalin raises the excitability and working capacity of the fatigued muscle.

Orbeli and his collaborators have also described changes occurring in the excitability of various structures of the central nervous system and the receptors under stimulation of the sympathetic fibres (disappearance of Sechenov's inhibition after section of the sympathetic chain, changes in the excitability of reflex arcs and receptors). There are indications of certain changes in the higher nervous activity observed for some time after the removal of the cervical sympathetic ganglion which gives off fibres to the brain (E. Asratyan).

These influences of the impulses transmitted along the sympathetic system (but arising as a result of the reflex activity of the nervous centres) on the excitability of the nervous centres and receptors, are possibly also due to the action of the sympathetic nervous system on the cerebral blood vessels.

The influence of impulses conducted along the sympathetic system on the efficiency of the skeletal muscles, which were discovered by L. Orbeli and his collaborators, are apparently of great importance to the muscular activity of the organism. Cases have been described in which under certain forms of so-called emotional stress animals (and human beings) performed very strenuous muscular work. The classical investigations of Sechenov showed (Sechenov performed his experiments mainly on himself) that fatigue, developed in man by work of a certain group of muscles, was largely eliminated if while these muscles rested a short time work was done by other muscles (Fig. 242). Fatigue is also eliminated by stimulation of certain receptors (for example, the cutaneous [Fig. 242] or taste receptors) while the work responsible for the fatigue is still done. After Sechenov these facts were fully corroborated. It is quite possible that the aforesaid effect which eliminates fatigue or retards its development involves reflexly arising impulses which are conducted to the skeletal muscles along the sympathetic system. Regrettably, the influence of the impulses transmitted to the muscles along the sympathetic nervous system in normal muscular activity of the integral organism is still unknown.

Trophic influences of impulses conducted along sympathetic system. Investigating the innervation of the heart. Pavlov found that the intensifying influences of the sympathetic nerve on the heart were due to trophic action, i.e., action which, being initially directed at the tissue metabolism of the heart muscle, apparently increased the accumulation of the substances consumed during the work of the heart muscle, and changed all of its vital properties.

Trophic influences should be understood as influences exerted on the entire supply of nutritive substances to the tissues, on the passage of these substances from the blood and tissue fluid into the tissues, and on their assimilation and transformation.

After these investigations of Pavlov a series of facts have been described showing the influence of impulses transmitted along the sympathetic nervous system on metabolism and nutrition of certain tissues. Excitation of sympathetic nerve fibres leads, in response to cooling of the body, to an increase in metabolism which is characteristic of chemical thermoregulation (L. Orbeli and A. Tonkikh). It has also been found that after section of the sympathetic fibres, which extend to the skeletal muscles and the heart, the desympathized tissue slowly recovers the normal content of glycogen and fats after fasting (Wertheimer). Orbeli thought that the influence of the sympathetic nervous system on the muscles was due to the metabolic changes produced by the excitation of the sympathetic fibres in the tissues it innervated. It is possible that the sympathetic impulses affect the excitability of the endings of the motor nerve (P. Nekrasov), which, however, does not exclude the probability of trophic influence on the myoneural synapse.

It would be hardly correct to assume that the trophic influence is exerted only by the impulses conducted along the neurons of the sympathetic nervous system. There are no reasons to oppose the influences of these impulses to those transmitted along the efferent nerve fibres whose excitation directly changes the activity of various effectors; no change in this activity is possible without changes in the chemical and physicochemical metabolic processes which produce this effect. It is quite probable that impulses transmitted along the parasympathetic system and motoneurons also exert a trophic influence.

Biological role of sympathetic innervation and adrenalin secretion. The activity of the sympathetic nervous system and of the medullar tissue of the adrenals, which secretes adrenalin, is not indispensable to life. Cannon removed the entire sympathetic trunk with all the sympathetic ganglia in dogs and cats and additionally extirpated one adrenal and denervated the other. After such an operation the animals, at first sight, differed from normal animals but little, but under extraordinary stress, for example, hard muscular work, bleeding or cooling, all sympathectomized animals showed much less endurance than normal animals (Fig. 243).

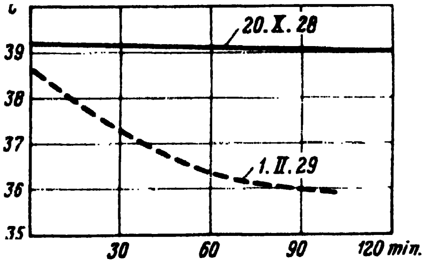


Fig. 243. Body temperature of (upper solid line) and sympathectomized (dotted line) cat in room with low temperature. Body temperature is indicated along ordinate, and time along the abscissa (after W. Cannon).

Impulses transmitted in the course of reflex activity along the sympathetic nervous system participate in the following processes: maintenance of the body temperature; increased coagulation of the blood under painful stimulation which may lead to injury; rapid redistribution of the blood by constriction of some vessels and dilation of others, and by changes in the state of the blood depots; acceleration and intensification of the heart beat; increase in the efficiency of the musculature; mobilization of the liver glycogen; modification of the secretion of the cutaneous glands which alters the resistance of the skin (provokes the so-called cutaneous-galvanic reflex discovered by I. Tarkhanov, i.e., changes the ohmic resistance of the skin under action of painful, strong sonic and other stimulations), etc. All these processes lead to a higher adaptability of the organism to the "extraordinary demands" made on it by changes in the external environment. The aforesaid effects are not produced by impulses transmitted along the sympathetic system alone, but in close interaction with the impulses conducted along the motor nerves and the parasympathetic system.

The impulses which reflexly arise in the centres under stimulation of exteroceptors and interoceptors and are transmitted along the sympathetic system to a number of effectors are also important for maintaining the constancy of the internal environment. This constancy of the internal environment is sometimes called *homeostasis* (Cannon). Thermoregulation, redistribution of the blood which depends on the constriction of certain vessels and simultaneous dilation of others, and on the activity of the blood depots, increased breakdown of glycogen in cases of low blood sugar—none of these processes can develop normally when the sympathetic system is excluded. But the efferent motor and parasympathetic neurons also play a big part in the maintenance of homeostasis; all processes of homeostasis are normally ensured by the equilibration of the organism with the environment which involves the activity of the higher part of the brain.

Influence of impulses transmitted by parasympathetic nervous system. The influences of the impulses transmitted along the neurons of the parasympathetic system to various effectors have already been considered in connection with blood circulation, respiration, digestion and excretion. Excitation may be distributed in various neurons of the parasympathetic system with great precision. For example, inhibition of cardiac activity may occur apart from the stimulation of gastric secretion, the influence on the movements of the intestines may be relatively independent of those on the secretion of the pancreatic gland, etc.

In the sympathetic system there is no such distribution of excitation among the separate groups of its neurons, and excitation reflexly arising in the centres usually spreads over many neurons of the sympathetic nervous system.

Effects of Excitation of Parasympathetic Nervous System

Nerve containing parasympathetic fibres	Organ upon which parasympathetic fibres act	Effect of excitation of parasympathetic fibres
N. oculomotorius	Musc. sphincter pupillae	Constriction of the pupil
Chorda tympani and n. Jacobsoni	Salivary glands	Secretion of saliva with low organic content
Vagus	Bronchioles	Constriction of bronchioles due to contraction of their musculature
	Heart	Deceleration of heart rate
	Stomach	Secretion of gastric glands
	Musculature of the stomach	Intensification of contractions and increase in tone
	Musculature of the intestines	
	Coronary vessels	Constriction
N. pelvicus	M. detrusor	Contraction
	M. sphincter urethrae	Relaxation

The effect of stimulation of the parasympathetic fibres often externally contrasts with the effect of isolately stimulated sympathetic nerve fibres. But the externally opposite influences exerted by excitation of the sympathetic and parasympathetic fibres on various aspects in the activities of different organs cannot serve as a basis for ascribing constant antagonism to the functions of the sympathetic and parasympathetic systems.

CHAPTER 57

FUNCTIONS OF THE SPINAL CORD

The spinal cord contains the cell bodies of all neurons whose axons innervate all skeletal muscles (except the muscles of the face), and the cell bodies of all preganglionic sympathetic fibres (the various segments of the spinal cord are connected with different skeletal muscles through the metamerism of root innervation); (see p. 556). Afferent fibres from all receptors of the skin and skeletal muscles (again except the receptors of the skin and musculature of the face), and from many receptors of the blood vessels, tissues and internal organs, enter the spinal cord. Owing to this, all motor reflexes (except the reflex contractions of the muscles of the face), most of the vascular reflexes, all reflexes of the urogenital system and of the rectum, all reflexes ensuring thermoregulation and those which regulate tissue metabolism of most tissues involve the spinal cord.

Consequences of Removal of Spinal Cord

With proper care the animals (dogs) in which the spinal cord was removed below the fifth cervical segment were kept alive for many months (Golz, Popov*). Removal of the spinal cord below the cervical segments paralyzes all the muscles of the body, except those of the head, neck and diaphragm, deranges thermoregulation and prevents reflex evacuation of the urinary bladder and intestines. Reflex activity is retained only in the upper part of the body: the animal breathes, takes food, masticates and swallows. But the organs of digestion, blood circulation and elimination continue to function even after the removal of the spinal cord (below C_6) and subsequent transection of the vagi, i.e., after the separation of the aforesaid organs from the central nervous system. Even reflex-humoral regulation of some functions of the organism is possible under these conditions because these animals partly retain the reflex regulation of the hypophyseal and thyroid secretion which ensures neuro-humoral regulation of the work of the kidneys, endocrine glands and uterus. (After removal of the spinal cord female dogs were artificially impregnated and gave birth to puppies.)

But the animal deprived of the greater part of its spinal cord is so greatly incapacitated that it could not live even a few days if the experimenter did not perform "for the animal" many functions irretrievably lost by the exclusion of reflex regulation. Such an animal is provided with easily assimilable food, kept in warmth and protected from any noxious influences; care is taken to ensure the evacuation of its urinary bladder and intestinal tract. As soon as this care is discontinued the animal dies.

The profound derangement of reflex activity itself in a certain measure contributes to the survival of the animals with the spinal cord removed (below segment C_6) and the vagi cut, since the almost complete cessation of muscular activity greatly limits the variations in the internal environment of the organism. In a normal organism these variations are equalized by extremely delicate reflex mechanisms which maintain the internal environment constant. In the crippled animal, deprived of the greater part of the spinal cord, these reflex mechanisms are very much impaired (although not fully excluded, because regulation of the functions of respiration and excretion is retained). The internal environment, too, changes here to a considerably lesser degree, owing to the exclusion of motor reflexes, and to the extremely monotonous conditions of existence, without which the animal with a shortened spinal cord cannot be kept alive.

After removal of the spinal cord some regulation of the functions of the internal organs is retained by the activity of the nerve cells scattered over many tissues (perhaps even in all of them).

Characteristics of Reflex Activity of a Spinal Animal

Normally the spinal cord always functions in connection with the higher divisions of the central nervous system. To study the activity of the spinal cord we must investigate its reflex activity after a transverse section which separates it from the brain.

After such operation no receptors or effectors, whose nerve fibres are connected with the spinal cord below the line of the cut, can participate in the acts which depend on the activity of the brain. A cut below the medulla

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* N. Popov managed to keep alive for a long time even such dogs in which, in addition to the removal of the entire spinal cord below the cervical segments, he severed both vagi and excised the entire chain of sympathetic ganglia.

oblongata separates the motoneurons of the respiratory muscles from the respiratory centre, and respiration ceases. Such an animal can be kept alive only for a very short time by artificial respiration. If the spinal cord is cut at the level of the sixth and seventh cervical segments, respiration continues by the respiratory movements of the diaphragm; the muscles of all extremities and the trunk contract only in response to stimulation of the receptors of those parts of the body which lie below the site of the cut. The muscles and organs which are innervated by the spinal neurons separated from the brain fail to react to stimulation of the receptors, whose afferent fibres enter the central nervous system above the point where the spinal cord has been cut.

At first sight the animal with a severed spinal cord does not differ from the animal with the spinal cord removed. A very important difference, however, between the spinal animal, i.e., the animal with its spinal cord cut at a certain level, and the animal with its spinal cord below that line removed, is easily observed.* This difference consists in the fact that the spinal animal invariably reacts with different reflexes to different stimulations of the receptors in the parts of the body situated below the point where the spinal cord is severed. These reflexes are called spinal reflexes; their reflex arcs close within the spinal cord of the spinal animal.

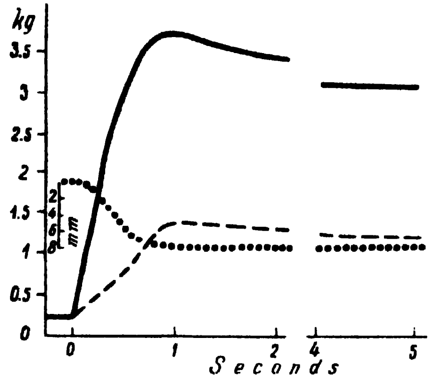

Fig. 244. Record of tension (solid line) developed by skeletal muscle in response to 8 mm-stretch (record of stretch is indicated by dotted line). Broken line indicates influence of stretch on muscle after transection of motor nerve; in this case slight increase in tension is conditioned by elastic properties of muscle itself. Scale of values of tension developed by muscle is along ordinate (after Denny-Brown, Creed, Eccles, Liddell and Sherrington).

It is possible to retain only one segment of the spinal cord and to remove all other segments which lie below and above it. In this case stimulation of the skin receptors, whose afferent fibres enter the spinal cord through the posterior roots of this segment, will provoke reflex contraction of the muscles innervated by the motor fibres of its anterior root.

The reflexes of the spinal animal are coordinated. Stimulation of each group of receptors (which does not result in irradiation of excitation) produces a definite reflex response. For example (Fig. 246), stimulation of the skin receptors of the foot by pinching provokes a reflex flexion of the stimulated leg with a simultaneous extension of the other leg; a slight tactile stimulation of the saddle-shaped part of the back evokes in spinal dogs the so-called scratch reflex which consists in a rhythmic movement of the foot towards the stimulated area of the skin; stimulation of the receptors of the urinary bladder or rectum by distention of these organs causes their muscles to contract reflexly.

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* In mammals the functions of the severed spinal cord, owing to phenomena of spinal shock, can be studied almost exclusively in chronic experiments. To facilitate the care for such spinal animals the spinal cord is usually cut below the second superior thoracic segment: after this operation the animal can move without assistance by its forelegs, and in a certain measure retains its thermoregulation. But in frogs, in which the phenomena of shock are short-lived and skin respiration ensures survival in the absence of pulmonary respiration, the spinal cord is more often cut below the medulla oblongata and the brain is removed; thus, of the entire central nervous system the animal retains only the spinal cord.

Stretch Reflexes

Stretching a skeletal muscle stimulates its receptors and causes it to react reflexly by a contraction.

Stretch reflexes were sometimes incorrectly called "proprioceptive reflexes."

If the skeletal muscle is stretched for a very short time (tenths or hundredths of a second), the resulting reflex contraction of the muscle is also transitory. Such a transitory stretch of the muscle is produced by a sharp tap on its distal tendon. For example, a light tap on the tendon of the quadriceps muscle (when the leg is bent in the knee) provokes the so-called knee-jerk reflex in which the leg is rapidly extended by a contraction of the quadriceps. When the muscle is protractedly stretched it responds reflexly by a protracted contraction; the stretch reflex is also called a myotatic reflex. This reflex is shown in Fig. 244.

The study of muscular bio-electric currents during a myotatic reflex shows that in a muscle as a whole only a small number of motor units contract at each moment and that the rate of impulses is not high (from 4 to 15 per second). In the course of the entire reflex contraction (which often lasts for many hours) the muscle fibres contract alternately.

In tendon myotatic reflexes the time of the transmission of excitation across the centres is so short (about 0.0007 of a second) that the nervous impulses can pass only through one synapse. This testifies to the fact that the little branchings of the afferent fibres, extending from the muscular receptors, can come in direct contact with the cell bodies of motoneurons innervating the muscle in which the given receptors are situated.

Tendon reflexes are accordingly characterized by a number of specific features: the phenomena of summation of excitation are weak (this is why a single stimulation of the receptors can provoke these reflexes); the refractory phase is short; phenomena of fatigue in the central part of the reflex arc are scarcely perceptible. Five, 10 or 15 quick taps on the tendon per second cause the muscle to reproduce this rhythm of stimulation and reflexly contract 5, 10 or 15 times per second; these contractions persist, barely weakening even after half an hour of stimulation. Myotatic reflexes, as before stated, may last for hours.

Significance of Stretch Reflexes

The muscular tone, which is a protracted tension of the skeletal muscles not accompanied by fatigue, is mainly based on myotatic reflexes produced by the stretching of the muscles. If the posterior lumbar roots of the spinal cord are cut in the frog on one side, the leg on this side is fully relaxed; but on the other side the leg is slightly bent owing to the tone of the flexor muscles which are stretched by the weight of the extremity. Muscles, temporarily deprived of sensibility through the injection of anaesthetics, also lose their tone.

Later we shall see (Chapter 58) that impulses are transmitted to the spinal neurons from the medulla oblongata, cerebellum and red nuclei of the midbrain; these impulses essentially modify the excitability of the neurons and affect the reflex responses of the stretched muscles. When the stretched muscles produce myotatic reflexes, the electric activity of the cerebral cortex changes. It has also been demonstrated that numerous combinations of any stimulus with a simultaneous light tap on the tendon develop a conditioned reflex: the corresponding muscle begins to contract under the action of the conditioned stimulus alone (for example, after a flash of an electric bulb) without any tap on the tendon of the muscle. These facts show beyond any doubt that the reaction to the impulses coming from the muscular receptors involves the cerebral cortex. Consequently, the reflex reactions of the motor apparatus to the stretch of the muscles depend on the activity of the entire central nervous system. A change in the state of any structure of the central nervous system, especially of the cerebral cortex, is reflected in the nature of the stretch reflexes, the tendon reflexes in particular (Fig. 245).

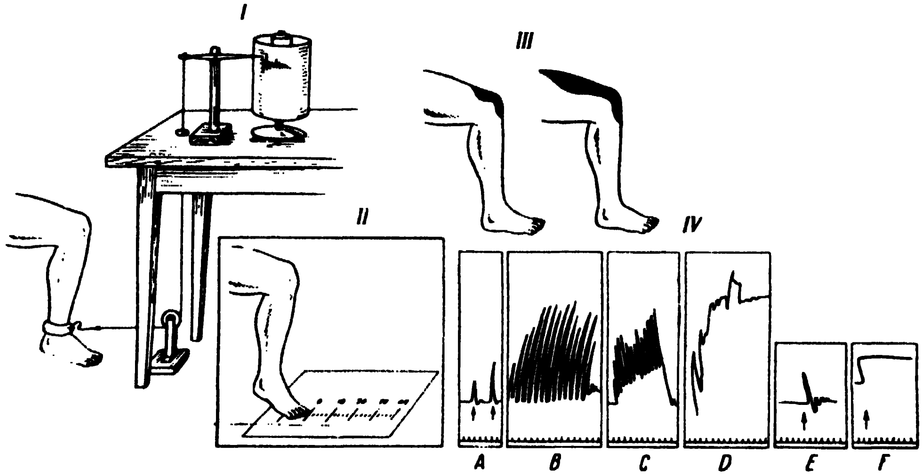


Fig. 245. Tendon reflex.

I—method of recording knee-jerk (tendon) reflex; *II*—method of measuring value of knee-jerk reflex by recording deflection of leg on scale; *III*—reflexogenous zone or receptive zone of knee-jerk reflex. Knee-jerk reflex is produced by stimulating this region by light tap of small hammer (left—normal location of this region in healthy child; right—in same child under strong emotional stress, for example, crying); *IV A*—record of knee-jerk in response to two taps with small hammer on tendon of quadriceps muscle (with interval of 3 seconds between taps); *IV B*, *IV C* and *IV D*—record of reflex flexions of leg produced by 20 to 30 taps on tendon, made at frequencies of 60 *(B)*, 120 *(C)*, and 300 *(D)* per minute. Summation of muscular contractions resulting in extension of leg, which persists during whole period of stimulations is observed under high frequency of stimulations; *IV E*—reflex contraction of quadriceps muscle which results from successive excitation in centres in response to stimulation by single tap on tendon (arrow); *IV F*—particularly pronounced successive excitation in centres leading to protracted extension of leg contraction of quadriceps muscle) in response to single tap on tendon (after N. Zimkin and N. Mikhelson).

It is probable that some of the so-called cutaneous-muscular reflexes, in which a light stimulation of the skin causes contraction of the muscles situated directly under the stimulated surface of the skin, are closely related to the myotatic reflexes. These reflexes include the scrotal reflex—contraction of the cremaster muscle as a result of stimulation of the inner surface of the thighs, and the abdominal reflex, which is a contraction of the ***rectus abdominis*** caused by the stimulation of the skin of the abdominal wall. These still inadequately known reflexes can, apparently, be reproduced for a very long time without fatigue, and, in the main, involve one rather than many muscles; their reflex arc may close in one or two spinal segments. It is quite possible that certain vascular reflexes and certain reflexes of the smooth musculature of the intestines, embracing only small sections of the blood vessels and intestinal tract respectively, have reflex arcs closing in one segment of the spinal cord. These reactions, however, are normally regulated by the activity of the entire central nervous system.

Intersegmental Reflexes of Spinal Cord

In the spinal cord, separated from the higher centres, a number of reflexes simultaneously involve several effectors which are supplied with efferent fibres from various segments of the cord. Such is the crossed extensor reflex in which extension of one extremity under stimulation produces flexion of the other extremity. Such is also the scratch reflex consisting in a rhythmic movement of the leg to the stimulated area of the skin. The same applies to the rhythmic, swinging movements of the extremities in which flexion of one leg is accompanied by extension of the other, after which the extended leg is flexed and the flexed leg is extended (these pendulous, alternating flexions and extensions of the extremities resemble the movements of the hind-legs of a walking animal).

All these reflexes necessarily involve the inhibitory process which ensures inhibition in the centre of the antagonistic reflex in each phase of the reflex act. While studying these reflexes P. Spiro, Sechenov's pupil, discovered the reciprocal inhibition of antagonists of the legs; this inhibition was subsequently studied by Sherrington.

Phenomena of reciprocal inhibition may, therefore, develop within the spinal cord alone. They are also always observed under normal conditions, when all motor acts are effected with the participation of the cerebral cortex (Chapter 64). As demonstrated by N. Wedensky during the flexion of the leg caused by stimulation of the motor zone of the cerebral cortex the flexors contract and the extensors relax on one side of the body, while reverse phenomena occur in the symmetric extremity (see Fig. 281).

The following are some of the spinal reflexes, whose reflex arcs usually include neurons of a number of segments of the spinal cord: a) motor reflexes evoked by the stimulation of the skin and muscular receptors. This group also includes motor reflexes arising in response to the stimulation of the interoceptors of the blood vessels and internal organs (viscero-motor reflexes); b) cutaneous-visceral and muscular-visceral reflexes, i.e., reflex changes in the activity of the internal organs and circulatory system produced by stimulation of the skin or skeletal muscles; c) viscero-visceral reflexes, which in response to stimulation of some internal organs or blood vessels give rise to reflex changes in other internal organs. This classification is quite conventional; it is designed to show the diversity of reflex reactions (even in a spinal animal). The conventional and schematic character of this classification consists in the fact that even in spinal animals it is difficult to encounter reflexes related only to one of the mentioned groups. For example, noxious stimulation of the skin reflexly evokes changes in the blood circulation, in the movements of the intestinal tract and contraction of the muscles of a spinal animal. Motor spinal reflexes caused by stimulation of the skin, for example, the flexor or scratch reflex, invariably include reflexes from the receptors of the contracting muscles which play an important role already in the coordination of the spinal reflexes.

The characteristic motor reflex reaction to a strong stimulation of the peritoneal receptors, manifesting itself in high reflex tension of the abdominal muscles, is simultaneous with a reflex change (inhibition) in the movements of the intestines. High reflex tension of the abdominal muscles during stimulation of the peritoneum is also observed when the connections between the spinal cord and the brain are normal and serves as an important symptom in diagnosing lesions of the peritoneum (this tension of the abdominal muscles is designated by clinicians as "muscular defence," "défense musculaire").

The best known spinal reflexes so far are the motor reflexes. Less is known about the reflexes of the circulatory, alimentary and excretory systems since they have hardly been investigated in experiments on chronic spinal animals. It has only been found that after transection of the spinal cord, vascular reflexes, which manifest themselves in constriction of the blood vessels and increase in the blood pressure under noxious stimulation, recover much later than various motor reflexes.

Mechanisms of Coordination of Spinal Reflexes

Each spinal reflex is usually evoked by the stimulation of only one group of receptors which form the receptive field of the given reflex. For example, the receptors of the urinary bladder form the receptive field of the urinary reflex; the receptors of the *glans penis* form the receptive field of the reflex of erection; the receptors of the skin areas on the leg of the frog (Fig. 246) are the receptive field of flexor reflexes, and those of the thigh and back, the receptive field of the rubbing reflexes; the receptors of the skin of the dog's back are the receptive field of the scratching reflex, etc. This means that impulses coming along the afferent fibres from the receptive field of each reflex to the spinal cord, in the end, excite only definite efferent neurons. For example, impulses from the receptive field of the flexor reflex excite in the spinal cord the efferent neurons of the flexor muscles, but do not stimulate the neurons of the smooth musculature of the urinary bladder or of the muscles of the anterior extremities. The intersegmental spinal reflexes produced by stimulation of the corresponding receptive field almost invariably involve the activity of different effectors, functioning in strict interaction and succession. For example, during the reflex of defaecation or urination a simultaneous reflex contraction of both hind extremities and an upward movement of the tail are observed; during the scratch reflex the leg which is brought to the stimulated area of the skin is rhythmically flexed and extended. This successive introduction of a number of effectors into the reflex act is probably due to the inclusion of new reflexes evoked from receptors stimulated during the preceding phase of the reflex act.

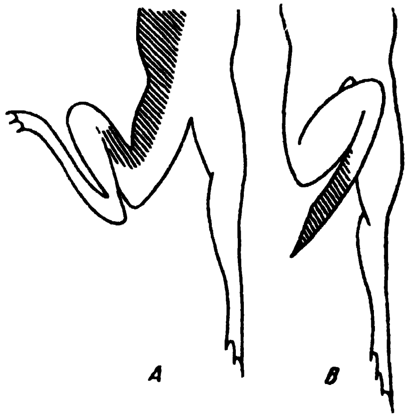


Fig. 246. Receptive zone of "rubbing" reflex (shaded *A*) and of flexor reflex (shaded *B*) in the frog (after Baglioni, with modifications).

The development of inhibition in the course of reflex activity is clearly revealed by graphic records of the motor spinal reflexes. Most of the skeletal muscles, even when the receptors are not specially stimulated, are in a state of tonic contraction produced by excitation which arises reflexly in the motoneurons in response to impulses constantly coming to the central nervous system from the muscular receptors and probably also from the cutaneous receptors. If the motoneurons of any muscle are inhibited, the tone of the latter is lost, and the muscle relaxes, which is shown in the myographic curve (Bronquist, Sherrington et al.).

Inhibition manifests itself in the discontinuance or prevention of excitation of the efferent neurons. This inhibition is, apparently, determined by the activity of internuncial neurons of the spinal cord (as far as reflexes of a spinal animal are concerned). The fact that the inhibitory processes arise mainly in the internuncial neurons is testified to, for example, by the following data. When protracted stimulation of an afferent nerve no longer produces a reflex response, the latter can be restored if the stimulation is transferred to another afferent nerve of the same receptive field.

The following experiment proves that inhibition necessarily develops in such a relatively simple form of reflex activity as spinal reflexes. By subjecting the motor nerve to maximal stimulation, it is easy to measure the maximum intensity of the contraction of the muscle which manifests itself when all its motor units are excited. It turns out, however, that separate or simultaneous stimulation of the afferent fibres of various nerves fails to produce a maximal reflex contraction of the muscle (Sherrington and his co-workers). Hence, the conclusion must be drawn that the process of inhibition prevents the propagation of impulses from the afferent fibres to all efferent neurons of every muscle. During a reflex contraction of the muscle produced by stimulation of various afferent fibres the process of inhibition is sometimes more and sometimes less pronounced, but never fully ceases.

Conditions of Constancy and Variability of Reflexes in the Absence of Cerebral Hemispheres. Principle of the Dominant

Each reflex act of the organism is always the same if reproduced under exactly the same conditions; any change in the responses of the organism to stimulation of the receptors is determined by a corresponding change in the conditions under which they are evoked. The facts relating to the constancy of the spinal and bulbar reflexes observed under very definite conditions and the similarly regular modification of reflexes resulting from changes in these conditions must be considered from this point of view.

It will be observed that the experimental material, which characterizes the laws of the reflex activity in the absence of the higher divisions of the brain, has been obtained mainly by a study of motor reflexes in spinal (or decerebrate) animals. But studies of the respiratory, vascular and secretory spinal reflexes, of reflexes involving the medulla oblongata and all reflexes in the so-called thalamic animal (Chapter 59), aimed at establishing the nature of the general mechanisms of reflex activity, have barely started.

Influence of Intensity of Stimulation on Nature of Spinal (and Bulbar) Reflexes

When stimulation of the receptors is intensified, the intensity of the reflex increases while its nature remains unchanged; for example, salivation increases (when stimulation of the taste receptors is intensified), the flexors of the leg contract with greater force in response to a stronger prick of the skin on the foot, etc. Still stronger stimulation of the receptive field of a reflex adds new effectors to the reflex which are not involved in reflex activity produced by weaker stimulation; as a result the reflex is generalized.

When irradiation of the reflex excitation in the centres is very high, the reflexes largely lose their adaptive significance, since the reaction involves a mass of diverse effectors (the movements of a drowning man, which in no way help him keep afloat, serve as an illustration). The reactions to very strong stimulations of different reflex zones may be similar (chaotic movements).

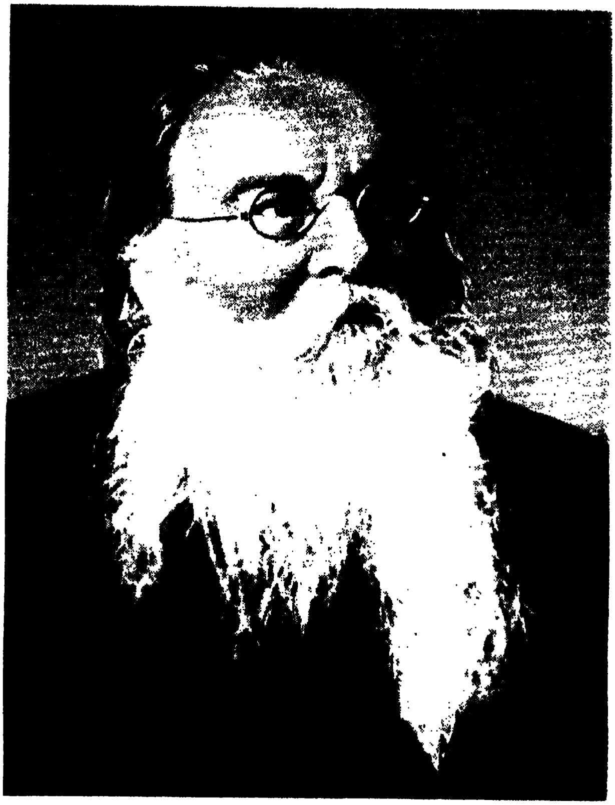
If stimulation of the receptors goes beyond a certain limit, the reflex activity of the effectors either diminishes, or is fully suppressed.

Inhibition may leave a protracted aftereffect and weaken or even fully suppress not only the reflex evoked from the stimulated receptors, but also reflexes from other receptive fields. Reflex activity is often inhibited by strong stimulation not during stimulation, but some time after its suspension, especially in animals with the nervous system intact and sometimes also in reflexes of animals with the spinal cord separated from the higher centres.

Any reflex can be intensified or inhibited depending on other reflexes which are evoked at the given moment or were evoked prior to it. But whereas some reflexes are very susceptible to changes, others yield to inhibitory influences with difficulty.

Reflexes whose reflex arcs include afferent fibres terminating directly on the bodies of the efferent neurons are the most stable. Such are the stretch reflexes (the knee-jerk and others). It is difficult to produce complete inhibition of such reflexes as the corneal reflex, pupilary reflex, scrotal reflex and the reflex of the *rectus abdominis* to the stimulation of the skin.

Principle of the dominant. A number of cases, which were characterized as variability of reflexes or as their "distortion," were explained by A. Ukhtomsky who advanced the principle of the dominant. Ukhtomsky proceeded from the proposition that the relations between various central structures (intercentral relations) depended both on the "history of the system" and on the stimuli acting upon it at the given moment, the variable relations between the centres always exerting an influence on the nature of the reflex act.



A. Ukhtomsky

The experiments on which this proposition was based consist, for example, in the following: if a reflex contraction of the extensor muscles is produced in the spinal frog several times in succession by stimulation of the receptive field of the rubbing reflex, stimulation of the receptive field of the flexor reflex does not produce flexion, but a stronger reflex contraction of the extensor muscles. Similarly, during the so-called embracing reflex in male frogs no stimulation of the skin provokes any movements, except a stronger reflex contraction of the muscles of the anterior extremities. By the term *dominant* Ukhtomsky therefore implied a focus of excitation in any division of the central nervous system that modifies the current activity of the nervous centres by attracting to itself impulses which in the absence of the dominant provoke a different reflex.

In his theoretical views Ukhtomsky based himself on Wedensky's theory of parabiosis. He found that the excited centre intensified the effect of its excitation at the expense of incoming "foreign" impulses only at certain degrees of excitation. If the excitation in a centre was so high that as a result of any further strengthening it passed into parabiotic inhibition (through its characteristic phases, p. 513), the impulses acting on the dominant centre would not reinforce the excitation of the dominant focus, but, on the contrary, would bring it to a state of inhibition.

The influence exerted by the dominant centre manifests itself in the activity of all divisions of the nervous system (Ukhtomsky's initial experiment established that stimulation of the motor zone of the cerebral cortex increased defaecation, prepared by the introduction of water into the rectum). Such phenomena were described earlier and designated as phenomena of "Bahnung," or "facilitation." But prior to Ukhtomsky the activity of the spinal cord was believed to depend on invariable properties of the neurons entering permanent reflex arcs. Ukhtomsky showed, however, that in the spinal cord, too, the reflex activity was dynamic and depended on the relations established during this activity between various nervous structures.

In the spinal cord (in higher animals—in all divisions of the central nervous system, except the cerebral cortex) changes taking place during the development of the dominant, *cannot last long*. For example, excitation in the central links of the urinary reflex in the spinal dog may be intensified, if the dog's paw is at that time stimulated by pinching; in this case pinching does not produce flexion of the paw, but intensifies urination. But when the receptors of the urinary bladder are no longer stimulated, this change in the flexor reflex disappears. However often flexion of the paw in the spinal animal is combined with distention of the urinary bladder, no pinching of its paw without any actual stimulation of the receptors of the urinary bladder or without its aftereffect will produce the urinary reflex. In the normal dog, however, it is easy to elaborate a conditioned reflex by combining the pinching of the paw with the distention of the urinary bladder after which pinching will produce contraction of the muscles of the urinary bladder even when the latter is not distended.

Phenomena of Spinal Shock

After a transverse section of the spinal cord, the formations, separated from the higher centres, are for some time unable to perform any reflex acts; the excitability of the spinal cord below the site of the section is suppressed. Gradually, within certain periods of time, the duration of which depends on the species of the animal, the reflex activity of the spinal cord is restored. The myotatic reflexes, particularly the tendon reflexes and the flexor reflex of extremities in response to painful stimulations of the foot (pricking, pinching), recover first. The extensor, urinary and vascular reflexes recover later (in dogs and cats within a period of 3 to 5 weeks after the severance of the spinal cord; in monkeys still later).

The suppression of reflex activity in the spinal cord separated from the brain by a transection, is designated as spinal shock. Shock phenomena do not depend entirely on the stimulatory influence of the transection of the spinal cord. This is proved by the fact that a second transection of the spinal cord, made below the first one and similarly stimulating its transected nerve fibres, does not produce a repeated shock (Sherrington). The phenomena of shock are chiefly determined by the exclusion of the influences which the higher divisions of the central nervous system normally always exert on the spinal cord.

Strictly speaking, after transection of the spinal cord reflex activity of its segments separated from the higher centres never establishes itself at a definite and invariable level. It keeps changing, though less perceptibly than during the first days after the operation, when it is in the process of recovery. There are certain indications (W. Cannon) that after transection of the spinal cord its partly denervated neurons (due to degeneration of the nerve fibres descending from the higher parts of the brain) become more sensitive to adrenalin and acetylcholine which circulate in the blood. This may play a certain role in the recovery of the reflex activity of the spinal cord after its severance from the brain.

Shock phenomena are the more pronounced, the more developed the higher divisions of the brain. In frogs the shock arising after transection of the spinal cord disappears in a few minutes; in the dog recovery of complex reflexes takes many days; in monkeys, weeks; and in man, months. It is true that the time of the disappearance of shock phenomena cannot be ascertained, since after transection of the spinal cord its activity is, apparently, never stabilized. The foregoing approximate periods pertain to the recovery of complex reflex movements (extension of one leg with simultaneous flexion of the other, vascular reflexes and swinging movements of the extremities).

The impulses coming from the medulla oblongata and the midbrain are the most important for the maintenance of the normal excitability of the spinal cord in cats and dogs. But the influences coming from the cerebral cortex are particularly important in man and higher monkeys. Destruction of two-thirds of the spinal cord in the cat by a cut from the dorsal surface will produce no shock unless the incision affects the pathways which connect the spinal cord with the nuclei of the vestibular nerves. In man, however, damage of the pyramidal pathways alone develops almost as deep a shock as transection of the entire spinal cord.

It was recently demonstrated (M. Durmishyan) that transection of the dorsal half (or only of the posterior columns) of the spinal cord (p. 581) in the region of the superior thoracic segment alone may produce almost as deep a shock as complete transection of the spinal cord. If a second transection of the posterior columns in the region of the cervical segments is made after the recovery of the activity of the spinal cord shock phenomena reappear. Durmishyan believes that in this case the shock is due to the irritation of the ascending pathways of the spinal cord. This is also evident from the fact that after a second more caudal transection of the posterior columns (for example, at the level of D_5), no shock phenomena are observed. Similarly, a preliminary application of cold or novocain to the region of the inferior cervical segments prevents the shock, provoked by transection of the posterior columns at the level of the upper thoracic vertebra. It may be assumed that powerful centripetal impulses from the site of transection create foci of pessimal inhibition, which deranges the normal influence of the brain upon the spinal cord.

Subordinative chronaxie. Disruption of the connections between the spinal cord and the medulla oblongata and mainly, apparently, the midbrain, leads to a characteristic modification of the chronaxie of the skeletal muscles and motor nerves; the chronaxies in spinal animals (dogs, cats) are higher than in animals whose spinal cord is connected with the midbrain. This likewise reflects the influence exerted by the flow of impulses from the reflex centres of the brain on the lower divisions of the central nervous system. It is also testified to by the fact that the summation of impulses from afferent fibres after the separation of the spinal cord from the brain differs from normal. To evoke a reflex in the spinal animal requires a more frequent succession of impulses in the afferent fibres or a large number of such impulses if the rhythm is the same.

Even in the frog, in which spinal shock is weak, the ability of the spinal cord to effect summation of impulses sharply declines after separation of the spinal cord from the medulla oblongata and the midbrain. As a rule, such a frog fails to react with the flexor reflex to a single induction-current stimulation of the afferent fibres which extend from the receptors of the web. But if the cerebral hemispheres are removed, while the medulla oblongata and the midbrain retain their connection with the spinal cord, the frog does react to this stimulation with the flexor reflex. The specific role of the midbrain in dogs, cats and rabbits is apparently its production of impulses which reflexly arise in response to any change in the position of the head and body, and largely determine the distribution of muscular tone.

Effects of spinal transection in man. A human being with the spinal cord completely severed by a wound or other injury shows scarcely any reflexes for a period of one to four weeks.

As the reflex activity in the transected spinal cord is restored, a so-called Babinsky's reflex, i.e., upward extension of the big toe on stimulating the plantar surface by a blunt object, makes its appearance; the abdominal muscles also exhibit early recovery by reflex contractions in response to stimulation of the skin of the abdomen. This is followed by recovery of the knee-jerk and other tendon reflexes; the flexor reflexes reappear next as feeble flexions only in response to stimulation of the foot at first and then as vigorous flexions on stimulating any point of the lower extremity. The knee-jerk recovers somewhat later than the Babinsky's reflex, but the crossed extensor reflex appears the latest; in spinal man it is never so pronounced as in the spinal dog. In general, extensor movements are scarcely observed in man after spinal transection, while a tone in the flexor muscles is often evident—the patient lies with his legs half bent.

After spinal transection man often shows considerable generalization of reflexes: both legs flex vigorously in response to weak stimulation of the skin of the leg.

Brown-Séquard's syndrome. Section of one side of the spinal cord results in the Brown-Séquard syndrome. This syndrome is determined by the fact that most of the descending corticospinal fibres, like the ascending fibres of pain and thermal sensibility, decussate, whereas the fibres of muscular and partly of tactile sensibility do not. The ability to move and to react to stimulations of the muscular receptors is accordingly lost on the side of the transection or lesion of the spinal cord, while pain and thermal sensibility is retained. Contrariwise, the opposite side retains the ability to move (since the mass of fibres of the pyramidal pathway decussate in the medulla), but pain and thermal sensibility are lost. Tactile sensibility somewhat decreases, but does not disappear on either side.

Some Clinically Important Reflexes

Normally there are neither "spinal reflexes," nor "spinal centres," since there are no reflexes which are normally effected by the spinal neurons *alone* without any influence of the higher divisions of the nervous system. Spinal reflexes and their centres may be regarded as actually existing only when the spinal cord is transected.

Neuropathology, however, used to designate those reflexes as spinal whose investigation made it possible to find the region of the spinal cord in which particular pathological changes occurred. The study of a number of reflexes warrants the conclusions, since these reflexes *necessarily involve* the neurons situated in definite spinal segments.

In some cases observations of the reflexes mentioned in Table 26 also offer some ideas about the activity of the higher divisions of the nervous system. This pertains, for example, to Babinsky's reflex which disappears at about the age of one year, if the motor zone of the cerebral cortex and pyramidal tract function normally; in adults it appears in hemiplegia (lesion of the motor zone of one hemisphere paralyzing the side opposite to that of the lesion). An excessive intensification of the knee-jerk reflex is also often observed; the reflex manifests itself in a series of extensions of the leg in response to one light tap on the tendon of the quadriceps muscle.

The basic reflexes studied by clinical medicine (including those connected with the activity of the medulla oblongata and the midbrain) are enumerated in Table 26.

Table 26

Some Reflexes Easily Observed in Man

Name of reflex	Stimulation evoking reflex	Nature of response	Central link of reflex arc
Pupillary	Sudden illumination of eye	Constriction of pupil	Midbrain
Corneal	Light touch of cornea	Closure of eyelids	Medulla
Tendon reflexes:			Segments of spinal cord:
a) Ulnar	Tapping on tendon of biceps	Flexion of arm, slightly bent in elbow	V-IV cervical
b) Knee-jerk	Light tap on patella	Extension of leg	III-IV lumbar
c) Achilles reflex	Tap on Achilles tendon	Plantar flexion	I-II sacral
Cutaneous reflexes:			
a) Abdominal:	Drawing line on skin:	Contraction of abdominal wall in region of stimulation	
Upper	above navel		VII-VIII thoracic
Middle	at level of navel		IX-X "
Lower	below navel		XI-XII "
b) Testicular	Drawing line on inner surface of thighs	Elevation of testicle	I-II lumbar
c) Plantar	Drawing line on sole	Flexion of all five toes	V lumbar – I sacral

Normal Functions of Spinal Cord

We still judge of the activity of the spinal cord only by its anatomical connections, by the consequences of its removal and the study of reflexes in spinal animals. Conclusions concerning the normal functions of the spinal cord were made mainly by using the latter method. It was thought, for example, that if pricking of the foot produced flexion of the stimulated paw both in normal and spinal animals, in an undamaged organism flexion also resulted only from the reflex activity of the spinal cord. Furthermore, if the extensor reflexes in spinal dogs were weaker than the flexor reflexes, the conclusion was drawn that the extensor reflexes normally involved the brain. Actually, however, *all* reflexes involve the integrated activity of the central nervous system.

Strictly speaking, we know very little about the *normal* activity of the spinal cord. We know, of course, that motor and vascular reflexes are impossible without the spinal cord; this fact is quite obvious even from morphological data alone. It is likewise obvious that the spinal cord functions not only as a conductor of impulses. We still know very little, however, of the concrete ways in which the higher centres exert their influence on the processes developing in various spinal neurons. This question has never even been posed in any investigation, so deep-rooted is the habit of mechanically including the data which characterize the reflex activity of the spinal cord separated from the higher centres into the concept of integrated reflex activity.

Meanwhile the question of the normal activity of the spinal cord cannot be answered merely by studying its functioning when it is transected. Theoretically there is only one thing to do: it is to make a thorough study of the bio-electrical currents led off from an intact central nervous system simultaneously to many oscillographs (to many of their inlet channels) from several pathways, from certain groups of spinal neurons, the cerebral cortex, the basal, mesencephalic, cerebellar nuclei, etc. Until now these methods have not even been applied in acute experiments. There are only some important indications that distinct electric potentials are recorded in the motor zone of the cerebral cortex, for example, during flexion of the paw; this testifies to the fact that impulses arising during spinal reflexes reach the cerebral cortex. These experiments do not explain, however, how the given impulses are transformed in the neurons of the spinal cord.

The importance of the foregoing questions is so great that we deemed it necessary to point them out. They must also be posed in relation to the activity of the medulla oblongata, midbrain and cerebellum, since our knowledge of these structures is based on experiments investigating the consequences of their extirpation or of their artificial stimulation.

Tracts of the Spinal Cord

The tracts of the spinal cord are bundles of fibres forming the so-called white matter of the spinal columns. The anterior spinal columns represent a mass of white matter situated between the anterior fissure of the spinal cord and the anterior roots; the lateral columns are formed of white matter enclosed by the anterior and posterior horns of the gray matter of the spinal cord and by the corresponding roots; the posterior columns represent white matter situated between the posterior horns of the gray matter and the posterior roots.

The ascending tracts of the spinal cord consist of bundles of nerve fibres which conduct impulses along the spinal cord to the higher divisions of the central nervous system.

The fibres of the ascending pathways are either axons of cells lying in the spinal ganglia, or axons of those nerve cells of the gray matter in the spinal cord, at which the branchings of the fibres of afferent neurons terminate.

Impulses from various receptors are transmitted in the spinal cord along different pathways. A mass of fibres, extending from the muscular receptors, pass the medial part of the posterior roots and upon entering the spinal cord form the *column of Goll* (*funiculus gracilis*) and the *column of Burdach* (*funiculus cuneatus*, Fig. 247). These columns make up the posterior spinal columns, which are formed by processes of the cells of the spinal ganglia ascending to the medulla oblongata; there, the fibres of these columns terminate at nuclei which also bear the names of Goll and Burdach. The cells of these nuclei project new fibres to higher centres. In addition to fibres extending from the muscular receptors the columns of Goll and Burdach also contain part of the fibres which extend from the cutaneous tactile receptors. Some of these fibres terminate in the gray matter of the spinal cord where they give off a number of collaterals.

The dorsal spinocerebellar tract, or Flechsig's column, is situated in the posterior external part of the lateral column of the spinal cord (Fig. 247). The fibres of this tract are axons of cells of the same side and partly of the opposite side of the spinal cord. These cells lie in the gray matter at the base of the posterior horn, forming the so-called Clarke's column. The fibres of the dorsal spinocerebellar tract terminate at the cells of the cerebellar cortex. The *ventral spinocerebellar tract,* or the column of Gowers (Fig. 247), passes in the anterior-external part of the lateral spinal column in front of Flechsig's column. The fibres of this tract are processes of nerve

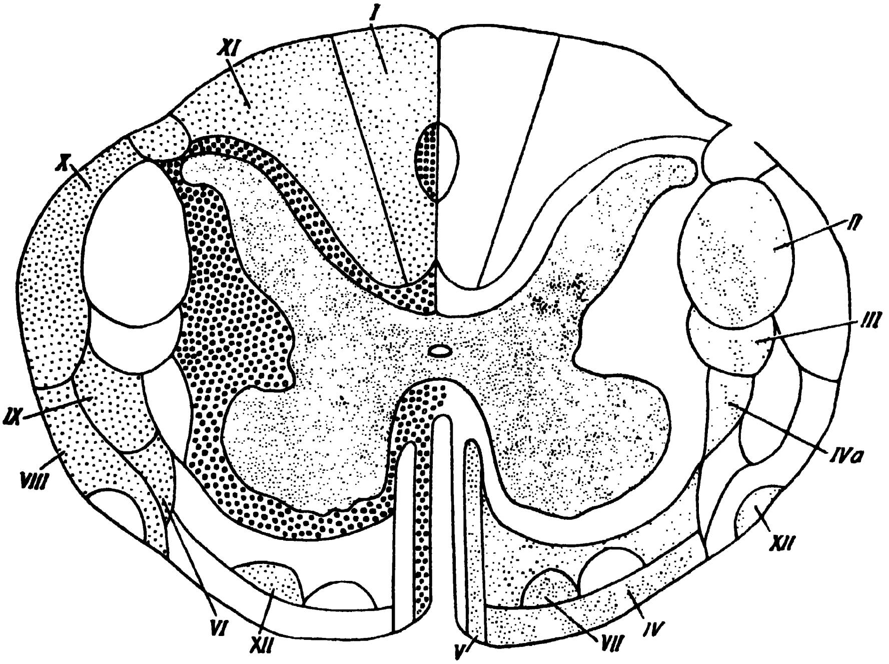


Fig. 247. Conducting pathways of spinal cord.

Dots on left indicate ascending pathways; on right, descending pathways. Circles show intersegmental pathways. *Ascending pathways: I* — column of Goll; *XI* — column of Burdach; *X* — Flechsig's dorsal spinocerebellar tract; *VIII* — ventral spinocerebellar tract of Gowers; *IX* and *VI* — lateral and ventral spinothalamic tract; *XII* — spinotectal tract. *Descending pathways: II* and *V* — lateral and pyramido-anterior tract; *III* — rubrospinal tract; *IV* — vestibulospinal tract; *VII* — olivospinal tract.

cells of the spinal posterior horns. Both spinocerebellar tracts, consequently, consist of axons of cells lying in the spinal gray matter. All fibres of the columns of Flechsig and Gowers conduct to the cerebellum the impulses which arise in the cells of the spinal cord under the influence of excitation transmitted to the centres from the muscular receptors.

Pain, cold, heat and partly tactile reception are transmitted by the fibres of the *spinothalamic tracts.*

The spinothalamic tract is formed by axons of small cells lying in the posterior horns of the spinal gray matter and lies in the lateral column to the interior of the spinocerebellar tracts. The nerve fibres, extending from the pain and thermal receptors, on entering the spinal cord, at once penetrate the matter of the posterior horns and terminate at cells which lie in the segment they enter. The small cells of the posterior horns, contacted by the fibres of pain and thermal reception give off axons which pass to the opposite side within the anterior white commissure and form the spinothalamic tract. The fibres which conduct impulses of thermal reception, apparently, lie dorsally from the fibres of pain reception.

In addition to the aforesaid ascending afferent pathways, there is also the *spinotectal tract* formed by fibres of the cells of the posterior horns which pass to the opposite side (the fibres of this tract terminate in the nuclei of the corpora quadrigemina).

The disposition of the pathways is shown in Fig. 247; their characteristic features are summarized in Table 27.

Table 27

Characteristics of Ascending Pathways in Spinal Cord

Names of tracts	Disposition of nerve cells whose axons form fibres of given tracts	Region where fibres of given tract terminate	Function	Notes
Fibres of posterior column (columns of Goll and Burdach)	Spinal ganglion	Nuclei of Goll and Burdach in medulla oblongata	Conduct impulses from receptors of muscles and tendons, and partly from receptors of tactile sensibility	Do not cross in spinal cord
Flechsig's spinocerebellar tract	Posterior horn of spinal cord	Cerebellum	Conducts impulses from receptors of muscles and tendons to cerebellum	In the main, do not cross in spinal cord
Gowers' spinocerebellar tract	ditto	ditto	ditto	In the main, cross in spinal cord
Lateral spinothalamic tract	Posterior horn of same segment which is entered by unmyelinated fibres of pain, thermal and partly tactile reception	Nuclei of thalamus opticus	Conduct impulses of pain and thermal reception	Cross in spinal cord (mainly, on level of entrance of afferent fibres)
Ventral spinothalamic tract	Posterior horn of any segment of spinal cord reached by fibres of tactile reception	ditto	Conduct impulses of tactile sensibility	Cross in spinal cord

From this review of the ascending pathways in the spinal cord it follows that in no case do the fibres of an afferent neuron, whose cell body lies in the spinal ganglion, ascend directly to the cortex of the cerebral hemispheres. The fibres of Goll and Burdach stop in their respective nuclei in the medulla oblongata, while all other fibres end at the cells of the posterior horns of the spinal cord on its different levels.

Thus, before reaching the cerebellum, thalamus opticus, olives or corpora quadrigemina the impulses from the receptors necessarily pass through at least two neurons: one neuron whose cell body lies in the spinal ganglion, and the second neuron with the cell body lying either in the nuclei of Goll and Burdach, or in the posterior horns of the spinal gray matter. The existence of more complex connections is not at all excluded. In particular, the fibres of the spinothalamic tract, apparently, project collaterals which again enter the gray matter of the spinal cord at different levels and form new synaptic junctions with its cells. It is possible that impulses of pain can also be conducted upward by the gray matter of the spinal cord.

The fact that tracts of different functional significance are isolated from one another is of practical importance. Transection of the spinothalamic tract often eliminates pain sensations on the side of the body opposite the transection. Surgeons sometimes utilize it (chordotomy) to relieve the patient from intractable pain which does not yield to any other therapy (it is true that in a number of cases even after transection of the lateral spinothalamic tract pain sensation does not entirely disappear owing to the existence of some roundabout pathways). Destruction of the gray matter of the spinal cord around its central canal similarly interrupts the pathways of pain sensibility. This occurs in the disease known as syringomyelia, in which pain sensations in metameres corresponding to the affected segments totally disappear, while tactile sensations persist.

The *intersegmental* tracts of the spinal cord represent more or less short fibres which do not reach the brain, but provide interconnection of various segments of the spinal cord.

Descending tracts connect the higher divisions of the central nervous system with the efferent neurons of the spinal cord. They include the *corticospinal* or *pyramidal* tracts, whose fibres are formed by axons of large pyramidal cells (Betz's cells) of the motor zone of the cerebral cortex. The greater part of the fibres of the pyramidal tract pass to the opposite side in the lower part of the medulla oblongata (decussation of the pyramids) and form the lateral corticospinal tract (crossed pyramidal tract) situated to the interior of Flechsig's column (Fig. 247) in the lateral spinal column. The lesser part of the fibres of the pyramidal tract forms the anterior corticospinal tract (direct pyramidal tract), whose fibres make up a narrow bundle lying in the anterior column of the spinal white matter. These fibres, however, also pass to the opposite side on the level of the spinal segment at which the given fibres terminate.

The cells of the motor zone of the cerebral cortex are thus connected by fibres of the corticospinal tracts only with the opposite side of the spinal cord. The fibres of the corticospinal tract terminate at the motor cells of the anterior horns which give off motor fibres to the skeletal muscles.

The higher the organization of the cerebral cortex, the more developed the pyramidal tract. It attains to its maximum development in man. Myelinization of the pyramidal tract ends only at the age of two.

The *rubrospinal tract* (Monakow) is formed by fibres which are processes of the cells of the red nucleus (*nucl. ruber*) of the midbrain. Already in the midbrain these fibres fully cross to the opposite side (the so-called Forel's decussation), and in the spinal cord extend to the anterior of the lateral corticospinal tract in the lateral spinal column (Fig. 247, *III*).

The fibres of the *tectospinal, olivospinal* and *vestibulospinal* tracts (Fig. 247) are also descending pathways. The fibres of these tracts are formed by the processes of cells lying in the tectum of the midbrain (tectospinal tract), in the olive (olivospinal tract) and in the lateral nucleus of the vestibular nerve (vestibulospinal tract).

The fibres of all the foregoing tracts run through the medulla oblongata. The medulla itself gives rise to a pathway which is an extension of Goll's and Burdach's columns and represents axons of cells lying in Goll's and Burdach's nuclei. Upon leaving Goll's and Burdach's nuclei these axons pass to the other side of the medulla oblongata (decussation) and enter the medial lemniscus (*lemniscus medialis*), which is also joined by the spinothalamic tracts. Higher (in the region of the pons) the medial lemniscus is adjoined by fibres of the lateral lemniscus extending from the nuclei of the auditory nerve. The medulla oblongata gives rise to fibres of the second neuron of the trigeminal nerve (*lemniscus trigemini*), which reach the optic thalamus, and to fibres connected with the nuclei of the vestibular and vagus nerves.

CHAPTER 58

FUNCTIONS OF MEDULLA OBLONGATA

Role of Reflex Activity of Medulla Oblongata

Afferent fibres entering the medulla oblongata include those which conduct impulses from the receptors of the skin of the face, mucous membranes of the eyes, nasal and oral cavities (with taste receptors), organ of hearing and labyrinths, the receptors of the larynx, trachea and lungs, heart, aortic and sino-carotid zone, and a number of receptors of the stomach, liver, pancreas and small intestine.

Impulses arising in the afferent neurons of the medulla ensure: a) defensive reflexes of the eye (winking, tear secretion); b) contraction of all the muscles of the face; c) secretion of the salivary and gastric glands and the pancreas; d) activity of the muscles of the tongue and larynx; e) regulation of cardiac activity and the movements of the alimentary tract.

Thus, reflex regulation of blood circulation, respiration and digestion, the reflex acts of all the muscles of the face and the reaction to stimulations from all receptors of the skin and mucous membranes of the face, eyes, mouth, larynx, oesophagus, stomach, intestines, organ of hearing, labyrinths and some of the most important interoceptors of the organs of the thoracic and abdominal cavities are possible only when the medulla oblongata functions normally. It follows that the medulla oblongata plays a tremendous role in the organism; injury to the medulla is often almost immediately fatal.

Role of Medulla in Regulation of Muscle Tone

If the brain of a mammal including the midbrain and its red nuclei is removed (Fig. 248, line *III*), but the medulla oblongata is retained and not separated from the spinal cord, high tension of the extensor muscles develops (Fig. 249) and persists for hours and even days. The extremities of such an animal are extended and can be bent only with great difficulty. The cervical muscles which bend the head backward are strained, the spinal column is somewhat arched (opisthotonos). Thus, all muscles whose tension opposes the action of the force of gravity (extensors) are in a state of protracted tonic tension after the separation of the medulla oblongata from the midbrain. This sharp increase in the tone of the extensor muscles was termed by Sherrington *decerebrate rigidity* (decerebration signifies removal of the brain above the medulla oblongata).

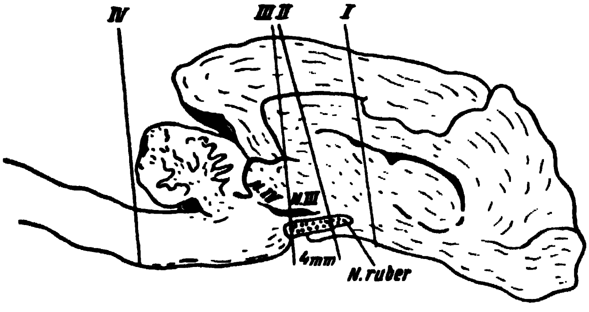


Fig. 248. Schematic diagram showing sections of brain stem in their relation to decerebrate rigidity. Sections *I* and *II* produce no rigidity (in front of n. ruber). Section *III* produces rigidity (behind n. ruber). Section *IV* terminates rigidity (after Magnus, with some modifications).

In decerebrate rigidity the tone of the extensors is higher than that of the flexors; but the latter are not relaxed either; owing to their protracted tension, the extremities become, as it were, rigid pillars able to support the weight of the body.

Decerebrate rigidity does not develop, if the midbrain of the animal retains its connection with the medulla oblongata (Fig. 248, section along lines *I* and *II*). It is also absent when the medulla oblongata is detached from the spinal cord (Fig. 248, section along line *IV*). It follows that in the medulla oblongata there are nerve cells which can bring the spinal neurons innervating the extensors into a state of excitation. But if the medulla oblongata is connected with the midbrain, no rigidity occurs; hence, the midbrain exerts influences that depress the excitation of the structures of the medulla oblongata which act upon the motoneurons of the extensor muscles.

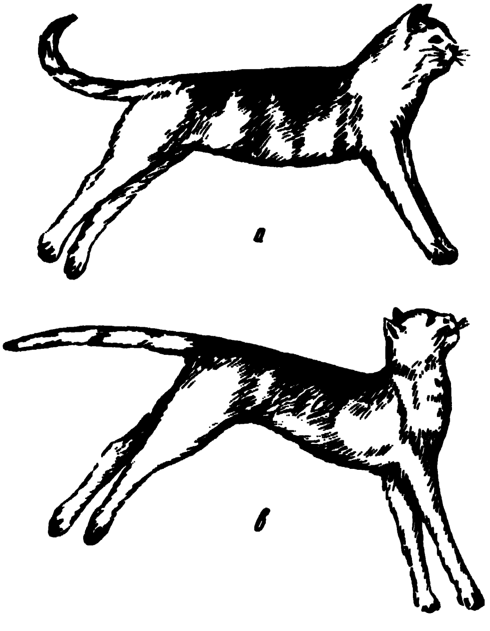


Fig. 249. Decerebrate rigidity.

a cat with excluded cerebral hemispheres (by the ligature of blood vessels); *b*- same cat with simultaneously excluded cerebellum (after Davis and Polak, from I. Beritov's book).

Increased tone of the extensors of the lower extremities is observed in human beings and apes when only the motor zone of the cerebral cortex is injured. In the upper extremities the tone of the muscles which oppose the force of gravity is also increased, but here such muscles are the flexors which flex the arm. But in man injuries to the midbrain also increase the tone of the extensors to a much greater extent than injuries to the cortex alone, and this increased tone of the extensors partly spreads to the upper extremities.

The reflex activity of the nucleus of the vestibular nerve plays an important role in the emergence of excessive tone of the extensors. Stimulation of the vestibular nucleus and, particularly, of its part known as Deiters' nucleus greatly reduces decerebrate rigidity; destruction of the *formatio reticularis* of the medulla oblongata together with Deiters' nucleus completely removes decerebrate rigidity.

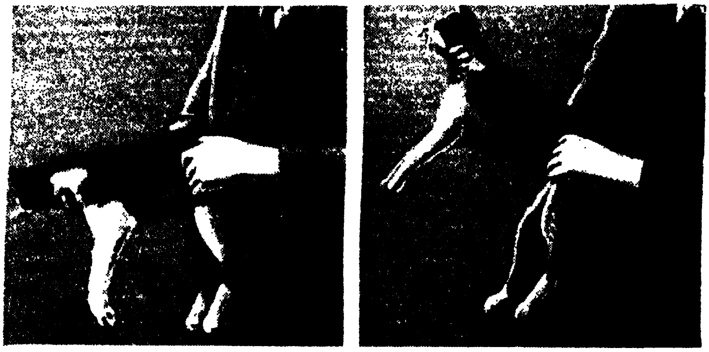


Fig. 250. Position of head producing minimal (*a*) and maximal (*b*) extensor tone (after Magnus).

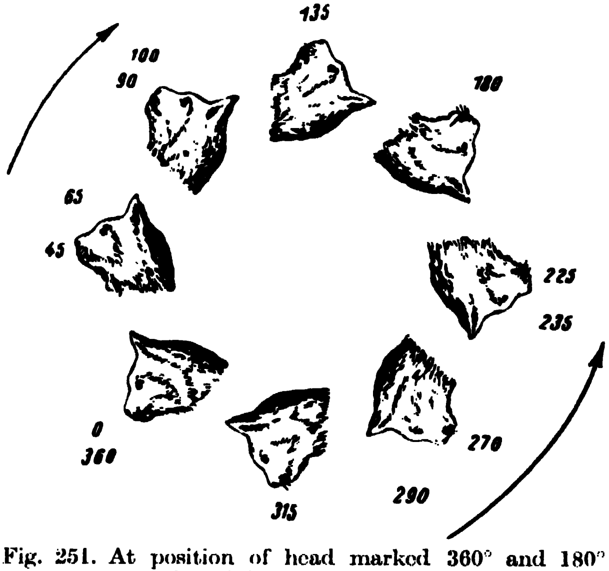


Fig. 251. At position of head marked 360° and 180° extensor tone is minimal; it rises to maximum at positions marked from 65 to 100° and from 290 to 235° (figures indicate degrees in relation to imaginary diameter of circle connecting figures 360° and 180°) (after Rademacher, from I. Beritov's book).

Decerebrate rigidity develops in response to impulses from the receptors of the extensor muscles. Injection of a solution of novocain into these muscles or transection of corresponding posterior roots suppresses the tone of the extensor muscles. Consequently, decerebrate rigidity arises as a result of abnormal intensification of reflexes effected by the spinal cord and medulla oblongata in response to the impulses coming both from the receptors of the extensor muscles, which are stretched by the action of the force of gravity, and from the receptors of the labyrinth.

The role of the medulla oblongata in effecting decerebrate rigidity is probably connected with the fact that it receives a continuous flow of impulses from highly important receptors of the respiratory and circulatory systems and from the labyrinths. That is probably why the medulla oblongata continuously acts upon the reflex centres of the spinal cord and increases their excitability. If the spinal cord is separated from the medulla oblongata, it never develops the excitability in which the tone of the extensor muscles, in response to impulses from their receptors, rises to a level that characterizes decerebrate rigidity.

Penfield, who succeeded in keeping cats alive for three weeks after decerebration, observed fluctuating rigidity in them. Relatively recently Keller observed no pronounced rigidity in decerebrate animals kept alive for an even longer period of time. I. Beritov is probably right in stressing the important part played by the stimulation, which spreads from the site of the transverse section of the medulla, in the development of rigidity. In any case the scheme of mere equilibrium between the influences inhibiting and exciting the extensor neurons is, of course, greatly simplified.

Tonic labyrinth reflexes. The tone of the extensor muscles (and to a certain extent also of the flexors) changes reflexly in response to stimulation of the receptors of the labyrinth. The receptors of this organ (details can be found in Chapter 71) are stimulated by changes in the position of the head and in the velocity of the body's motion in space. The reflexes originating in the labyrinth receptors during changes in the position of the head are particularly important for the regulation of the muscle tone. In experiments performed on decerebrate animals Magnus found that the tone of the extensor muscles is maximal if the animal is placed in a position in which its snout is raised 45 degrees to the horizontal plane (Figs. 250 and 251). In this position of the head, the otolith of the *utriculus* hangs by the finest hairs of its epithelial cells (Chapter 71). In other positions of the head the extensor tone diminishes; it falls to a minimum when the animal is placed on its belly so that its mouth cleft is lowered 45 degrees to the horizontal plane (Figs. 250 and 251). The otoliths of the internal ear in this case lie on the hairs which support them. The extensor tone may even give way to flexor tone. Thus, excitation in the receptor apparatus of the labyrinths of the internal ear is at its maximum when the hairs of the otoliths are stretched, which leads to the maximal tone of the extensor muscles. Contrariwise, the extensor tone is minimal when the head is in a position in which the otolith lies on the hair that supports it.

Labyrinth reflexes fix the limbs in definite positions and were therefore named by Magnus *postural reflexes.*

Tonic reflexes from receptors of neck muscles. The labyrinth reflexes are not the only ones that influence the tone of the skeletal muscles. The impulses arising in the receptors of the neck muscles play the same role.

Any alteration in the position of the head usually affects the position of the head in relation to the trunk (and vice versa). To study pure labyrinth and neck reflexes, it is therefore necessary to experiment either on animals whose labyrinths have been removed (in which case only the neck reflexes are present), or on animals with the three upper posterior cervical roots transected on both sides (then afferent impulses from the receptors of the neck muscles are excluded, and labyrinth reflexes alone can be observed).

The influence of the neck reflexes manifests itself in the fact that when the head is turned from right to left or from left to right in relation to the trunk, the extensor tone is maximal on that side of the body towards which the top of the head is turned. If the head is turned on an axis, mentally drawn through both auditory meatuses, forward bending of the head causes increased extensor tone in the hind limbs, with reduction of tone in the fore limbs. Contrariwise, when the head is thrown backwards, the extensor tone in the fore limbs increases and the hind limbs flex.

Labyrinth reflexes to neck muscles. The neck and labyrinth tonic reflexes are interconnected because impulses from the labyrinths influence the tone of the neck muscles. The maximal tone of the neck muscles is observed in such positions of the head in which impulses from the labyrinths lead to a reflex increase in the extensor tone of the limbs. Impulses from each labyrinth influence mainly the neck muscles of the opposite side (therefore, when the labyrinth is damaged, the head of the animal is turned towards the side of the damage).

Significance of postural reflexes. In the normal organism regulation of the tone of the skeletal muscles is never confined to bulbar reflexes alone. The role of these reflexes, however, may also be detected in the normal animal. Let us recall, for example, the behaviour of the cat when meat is shown to it from above: looking at the meat the cat lifts its head and its neck muscles stretch, while its fore limbs extend and its hind limbs flex reflexly. If the receptors of the neck muscles are disconnected from the spinal cord by transection of the three upper posterior cervical roots, this reflex change in the tone of the limbs disappears: the cat lifts its head when it is shown meat, but the forelegs do not extend.

CHAPTER 59

FUNCTIONS OF MIDBRAIN, CEREBELLUM AND DIENCEPHALON

No efferent nerve fibres issue from the central nervous system above the midbrain; similarly, no afferent nerve fibres enter the central nervous system here except the fibres of the optic and olfactory tracts. In view of this, the higher divisions of the brain can be characterized as a mass of

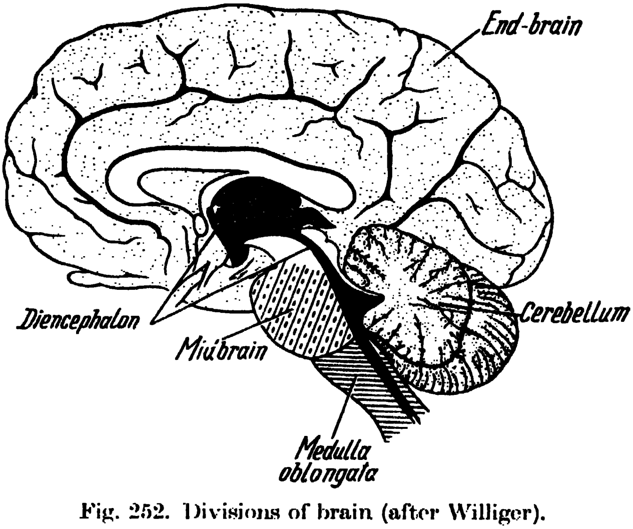


Fig. 252. Divisions of brain (after Williger).

neurons that form a superstructure on other neurons, which directly receive stimulations from the receptors, and on efferent neurons.

To comprehend the evolution of the cerebral hemispheres requires a consideration of the embryonic development of the central nervous system. It is well known that the nervous tube, which arises at an early stage of embryonic development, soon forms two divisions: the spinal cord and the brain. The latter division in its turn divides into three vesicles: the anterior brain, the midbrain and the rhombic brain. Later the first and third vesicles again subdivide into two vesicles each, thus forming five divisions in all: 1) the end-brain, 2) the diencephalon (these two divisions develop from the forebrain), 3) the midbrain, 4) the hindbrain, and 5) the medulla oblongata (the last-named two divisions develop from the rhombic brain). The end-brain forms a twin organ—the cerebral hemispheres. Their thickened ventral and lateral walls form the corpus striatum, while the remaining, thinner part of the walls forms the cerebral cortex. The diencephalon of the adult consists of the *thalamus opticus* and the nuclei of the hypothalamic region. The midbrain includes the four eminences (*corpora quadrigemina*), red nuclei, *substantia nigra*, and other formations; the hindbrain includes the cerebellum and the pons (Fig. 252).

Structures of Midbrain

The following structures belong to the midbrain:

a) the *cerebral peduncles* containing the conducting pathways from the lower centres to the higher centres of the brain and from the higher centres to the spinal cord and medulla oblongata. These conducting pathways also form the cerebellar peduncles;

b) *nuclei of the third and fourth pairs of cranial nerves*, whose functions are discussed in Chapter 70 devoted to vision;

c) *corpora quadrigemina*, containing groups of nerve cells essential for the coordination of the visual and auditory reflexes: turning the eyes and the head in the direction of optic stimulations, turning the head in the direction of acoustic stimulations. The removal of the corpora quadrigemina deranges these reflex movements. The anterior corpora are required for the reflexes from the receptors of the retina; the posterior corpora, from the receptors of the cochlea. Stimulation of the region of the corpora quadrigemina evokes movements of the eyes; pilomotor effects and contractions of the muscles of the vocal chords have also been described;

d) *substantia nigra*—a group of cells of the midbrain, whose functions are as yet unknown, but are apparently connected with the regulation of movements. At present most of the researchers relate the *substantia nigra* to the so-called extrapyramidal system;

e) red nucleus, *nucleus ruber*—a large aggregation of nerve cells in the midbrain (Fig. 248). The red nucleus contains a group of large and a group of small cells. It is connected by pathways, on the one hand, with the cerebellum and the nuclei of the *corpus striatum*, and, on the other hand, with the spinal cord (rubrospinal tract, Fig. 247). The red nuclei with the *formatio reticularis* surrounding them are undoubtedly involved in the regulation of muscle tone; this can be seen by comparing the behaviour of a decerebrate animal, in which only the pons, the cerebellum and the lower section of the midbrain, *situated below the region of the red nuclei*, are connected with the spinal cord and the medulla oblongata, with the behaviour of the so-called thalamic animal, in which the cerebral cortex and subcortical ganglia have been removed, while the midbrain with its red nuclei and the optic thalamus have been left intact and have retained connection with the medulla oblongata. The difference in the behaviour of the aforesaid animals can be seen from the following comparisons:

Decerebrate animal (cat or dog) in which only spinal cord and medulla oblongata are retained	Thalamic animal (cat or dog) in which midbrain and part of diencephalon are retained
High decerebrate rigidity	No decerebrate rigidity
Unable to move without asistance	Can rise without assistance
Only reflex regulation of muscle tone is observed (postural reflexes) which ensures maintenance of definite posture	Reflex regulation of skeletal musculature is observed (righting reflexes) which ensures transition from one posture to another
Maintenance of equilibrium is impossible	Maintenance of equilibrium is possible
Normal temperature of body cannot be maintained	Normal temperature of body can be maintained
Respiration is deranged	Respiration is normal

The nervous structures of the midbrain can be characterized, in general, as the simplest among the higher centres which coordinate the motor acts. The midbrain should be rightfully related to the higher structures, since the effect of its activity, like in all higher centres, is attained through influencing the executive neurons of the spinal cord and the medulla oblongata. At the same time they are the simplest nervous structures, in so far as normally their functioning fully depends on the higher divisions of the central nervous system, and they transmit to the executive neurons impulses (which, we may take it, are in some way or other transformed by them), arising in the cerebral cortex, or involving the latter. From the cerebral cortex these impulses are directed to the region of the red nuclei, *substantia nigra,* and corpora quadrigemina mainly through the striopallidal system.

The fact that *righting reflexes* are feasible in response to stimulation of the receptors of the skin and musculature, if the region of the red nuclei is intact, shows that the centres of the midbrain influence the neurons of the lower levels. The cat, in which the cerebral hemispheres have been removed, but the red nuclei with their surrounding reticular substance retain connection with the medulla oblongata and the spinal cord, stands up when laid on its side. Excessive excitation of the extensor muscles of the limbs, which is characteristic of decerebrate animals, is suppressed by influences from the region of the red nuclei, owing to which no decerebrate rigidity is observed when the latter are intact. At the same time, when the cerebral cortex and basal ganglia are intact, these righting reflexes are fully subordinated to the influences of the higher divisions of the brain. Normally these reflexes form a component part of the complex conditioned-unconditioned reflexes.

Functions of Cerebellum

Structure of cerebellum. The cerebellum is an organ which first appears in lower fish and is functionally highly developed in birds and mammals. Ontogenetically it belongs to the hindbrain, since in the embryo it develops from the wall of the fourth ventricle; a part of the cerebellum is closely connected with the nucleus of the vestibular nerve. The cerebellum of higher animals is made up of the phylogenetically older cerebellum (paleocerebellum—*lobus flocculus* and *nodulus)* and the new cerebellum (neocerebellum) which, in the main, is formed by its lateral lobes (represented in white in Fig. 253). The paleocerebellum is the part where the conducting pathways issuing from the vestibular nucleus and spinal cord terminate (Fig. 253).

The afferent connections of the cerebellum are shown in Figs. 253 and 254. Impulses come to the cerebellum from the spinal cord, vestibular nucleus, olives, centres of corpora quadrigemina, and cerebral cortex. Fibres from the nucleus of the vestibular nerve enter the *nodulus* and *lobus flocculus*; not only the axons of the cells of the vestibular nucleus, but also some fibres of the vestibular nerve proper ascend here. Afferent fibres from the medulla oblongata enter the cerebellum within the *corpus restiforme*. Afferent fibres from the spinal cord (fibres of the columns of Gowers and Flechsig) terminate in three posterior parts of the anterior lobe and two lower parts of the posterior lobe of the cerebellum (Fig. 254).

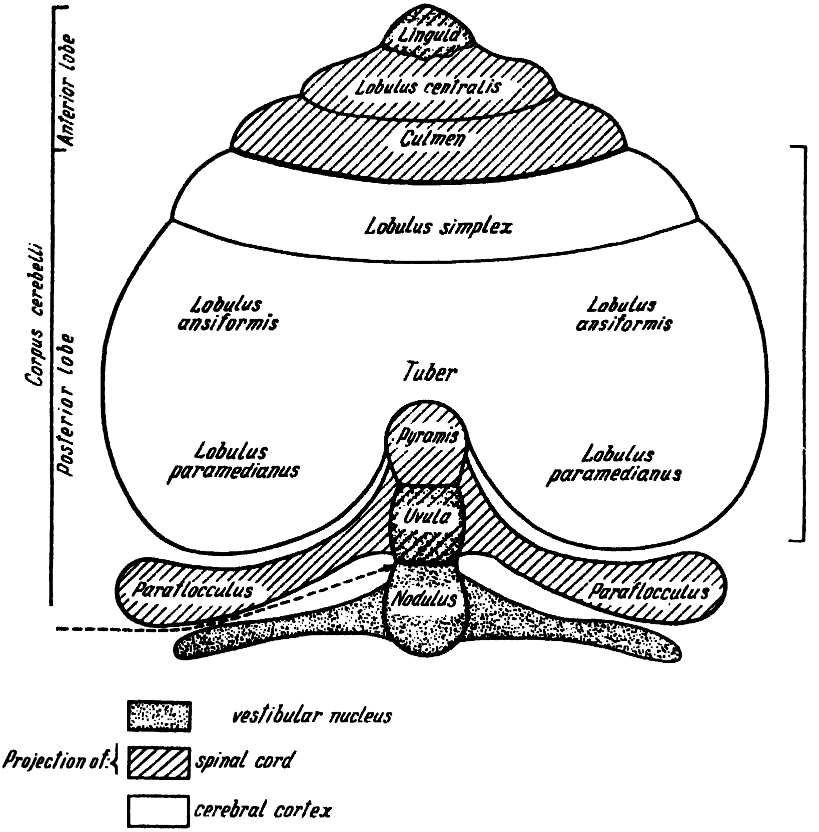


Fig. 253. Divisions of cerebellum and their afferent connections (after Dow).

Impulses arising in the muscular receptors and labyrinths go along the neurons of the spinal cord and medulla oblongata to the cortex of the cerebellum; among the nerve cells of the latter the cells of Purkinje may be regarded as efferent. The axons of these cells reach the nuclei of the cerebellum. Some of the cells of these nuclei give off axons which run to the optic thalamus (from where new fibres extend to the cerebral cortex), while axons of other cells of the cerebellar nuclei enter the red nuclei, the olive and the vestibular nucleus of the medulla oblongata; the axons of the cells of the red nucleus, olives and vestibular nucleus descend to the spinal cord along the rubrospinal (Monakow), olivospinal and vestibulospinal tracts and act on the motoneurons of the anterior horns.

These connections of the cerebellum suggest the idea that the function of its cortex consists in reflex action on the motoneurons (through the

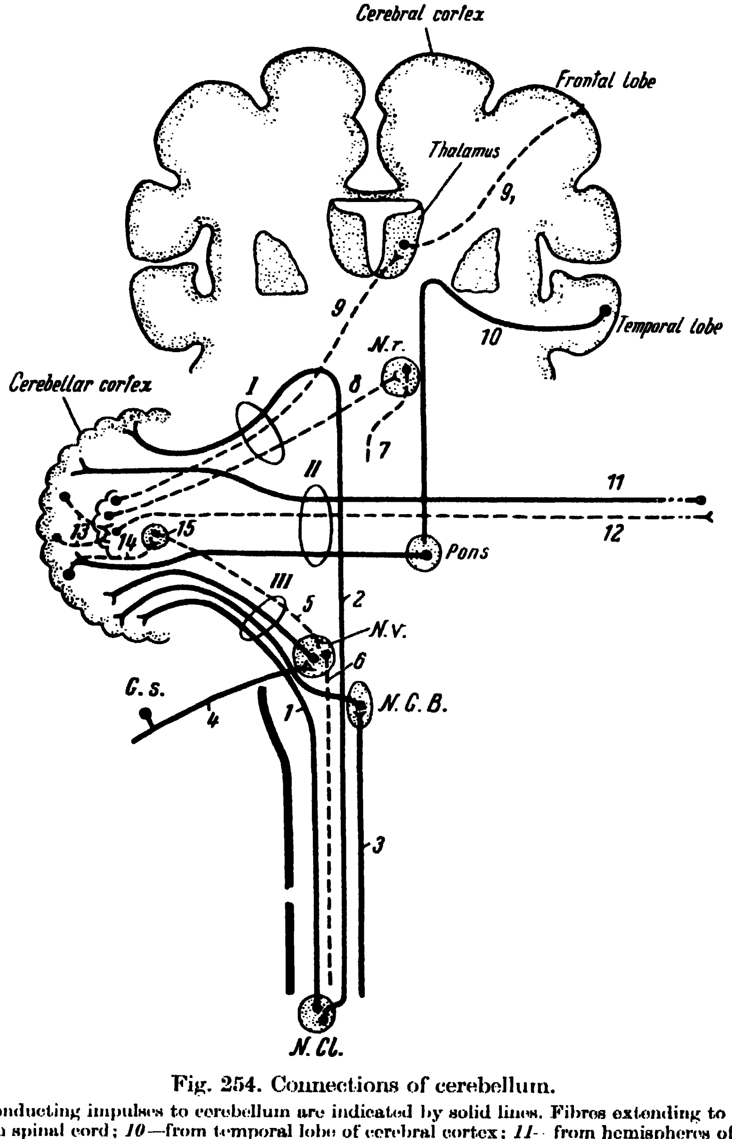


Fig. 254. Connections of cerebellum.

Pathways conducting impulses to cerebellum are indicated by solid lines. Fibres extending to cerebellu *1, 2, 3*—from spinal cord; *10*—from temporal lobe of cerebral cortex; *11*— from hemispheres of cerebellu on opposite side. Fibres transmitting impulses from cerebellum are indicated by broken lines; *9* and 9_1 pathways to cerebral cortex via thalamus opticus; *8*—pathways to red nucleus and thence to spinal co by way of Monakow's tract *(7)*; *5* pathways from cerebellum to vestibular nucleus *(N. v.)* and then along vestibulospinal tract *(6)* to spinal cord; *12* pathways to opposite hemisphere of cerebellu *13* fibres from cortex of cerebellum to its nuclei; *14* nucleus dentatus; *15* nucleus fastigii. *I, II* and *III*—superior, middle and inferior peduncles of cerebellum. *N. v.* vestibular nucleus; *N. G. B.*—nuclei of Goll and Burdach; *N. Cl.* —nuclei of Clarke's column (affere fibres from receptors of skeletal muscles and tendons lead up to its cells); *4*—fibres of vestibular nerv *Pons*—nuclei of the pons; *G. s.*—spiral ganglion (after Best and Taylor).

nuclei of the cerebellum and the red nuclei) in response to stimuli coming to the cerebellum from the receptors of the muscles. The cerebellum performs its functions in connection with motor impulses arising in the cerebral cortex. This is testified to by the existence of connections between the neocerebellum and the cerebral cortex. The above supposition is, in general, supported by experiments and clinical data; when considering them, it is always necessary to distinguish between the paleocerebellum and the neocerebellum.

Functions of cerebellum. Removal of the cerebellum leads to very specific derangements in the coordination of movements (ataxia), characterized by a disproportion between the intensity of contraction of various muscle groups and the nature of the movements performed: in walking the legs are raised high and placed wide apart; large swinging movements of the limbs and head are also observed; for example, before putting its snout into the food receptacle the dog lowers and raises its head several times. Injuries to the neocerebellum reduce the muscle tone in monkeys and man (atonia), animals become easily fatigued (asthenia—loss of strength).

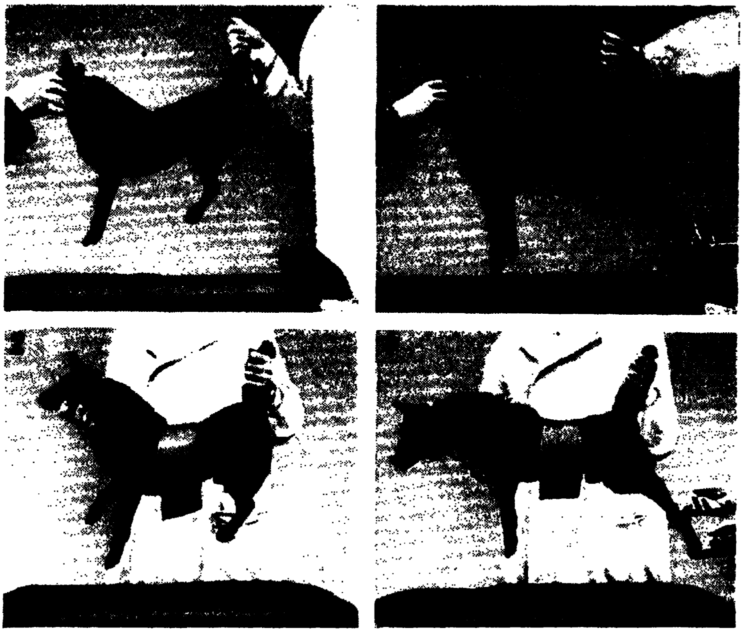


Fig. 255. Tension of extensor muscles in the dog deprived of cerebellum. Pictures *3* and *4* show increased tone during stimulation of foot (after Rademacher).

The functions of various parts of the cerebellum in higher animals differ. Extirpation of the paleocerebellum (*nodulus* and *flocculus*) results in a loss of body equilibrium similar to that produced by injuries to the labyrinths. Removal of the anterior lobes of the cerebellum increases the tone of the extensor muscles and intensifies the tendon reflexes (Fig. 255). Under decerebrate rigidity stimulation of the anterior lobes of the cerebellum sharply lowers the tone of the extensors, whereas removal of the cerebellum intensifies decerebrate rigidity (Fig. 255).

Stimulation of the *culmen* decreases the extensor tone of the fore limbs; stimulation of the *lobus centralis*, that of the hind limbs; and stimulation of the *lobus simplex*, that of the muscles of the neck. In the *lingula* there is, apparently, a projection of labyrinth fibres; stimulation of this anterior part of the cerebellum inhibits the labyrinth reflexes.

Studies on monkeys have shown that the cutaneous and auditory analysers are represented in the cerebellum, since tactile stimulation of the skin modifies the electrical activity in the *lobulus paramedianus*, and acoustic stimulation influences the nature of bio-electric currents in the vermis. Stimulation of the skin of various parts of the body leads to alterations in the bio-electric currents in different parts of the cerebellar cortex (Fig. 256).

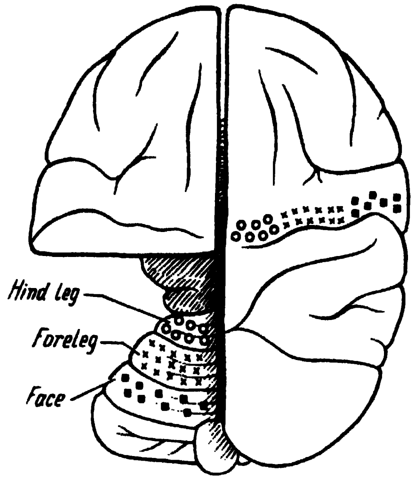


Fig. 256. Localization of functions in cerebellar cortex.

Circles, crosses and squares on left indicate sections of cerebellum where action currents manifest themselves during stimulation of the hind- and forelegs and surface of monkey's face; same symbols on right indicate sections of cerebral cortex (precentral convolution), whose stimulation likewise produces action currents in sections of cerebellum having analogous symbols (after Adrian, from Fulton's book).

Electrical phenomena in the cerebellar cortex also change when the cerebral cortex is stimulated (Adrian). Stimulation of various sections of the motor zone of the cerebral cortex shows changes in the electrical activity of the same sections of the cerebellar cortex in which action currents arise in response to the stimulation of the paws and muzzle (Fig. 256).

The connections between the cerebellum and the cerebral cortex are bilateral—from the cerebellum to the cerebral cortex, and from the latter to the cerebellum (through the pons, thalamus, and, probably, also the nuclei of the fore- and midbrain). These connections are characteristic of the neocerebellum. It is probable that impairment of these connections deranges the complex motor reflex acts in injuries to the cerebellum. In the latter case oscillatory movements of the head and limbs are observed; a patient with a cerebellar lesion finds it difficult to bring a spoon to his mouth; when his hand holding the spoon comes about half-way to the mouth, it begins to move in the opposite direction. A movement once started, cannot be stopped, i.e., inhibited, which in the terminology of the theory of conditioned reflexes (actually not yet applied to the analysis of cerebellar lesions) means pathological inertness of the excitatory process in the motor analyser of the cerebral cortex.

Disorders caused by cerebellar lesions are gradually compensated, this compensation fully depending on the activity of the cerebral cortex. Many months after removal of the cerebellum, the dog deprived of the cerebral cortex walks as clumsily with its legs wide apart, keeps balance with as much difficulty and moves with as much coarse tremor as in the first days after extirpation of the cerebellum (E. Asratyan).

While stimulating the cerebellum and after its removal L. Orbeli and his collaborators discovered a number of changes in the functioning of the internal organs. The mechanism of cerebellar participation in regulating the activity of the internal organs is not clear as yet.

Functions of Nuclei of Hypothalamic Region

The hypothalamic region (hypothalamus) consists of the nervous structures of the diencephalon separated by a small fissure from the optic thalamus and is made up (Fig. 257) of a number of nuclei (*nucl. paraventricularis, nucl. supraopticus, tuber cinereum, copr. mammillaria,* etc.).

Impulses from receptors enter the nuclei of the hypothalamic region mainly from the thalamus, through which fibres from the olfactory, premotor and motor zones of the cerebral cortex, and, probably, from its other zones, pass to the hypothalamic region. Before reaching the hypothalamic region these fibres extending from the cortex are interrupted at the cell bodies of the neurons of the *globus pallidus* and the thalamus; the axons of the neurons of the *globus pallidus* and thalamus enter different nuclei of the hypothalamus (Fig. 257). There may be direct connections between these nuclei and the cerebral cortex, particularly between these nuclei and the phylogenetically oldest part of the cerebral cortex—the olfactory lobes.

Fibres emerging from the nuclei of the hypothalamic region descend to the midbrain, medulla oblongata and spinal cord, terminating on cells whose axons form preganglionic fibres of the vegetative nervous system.

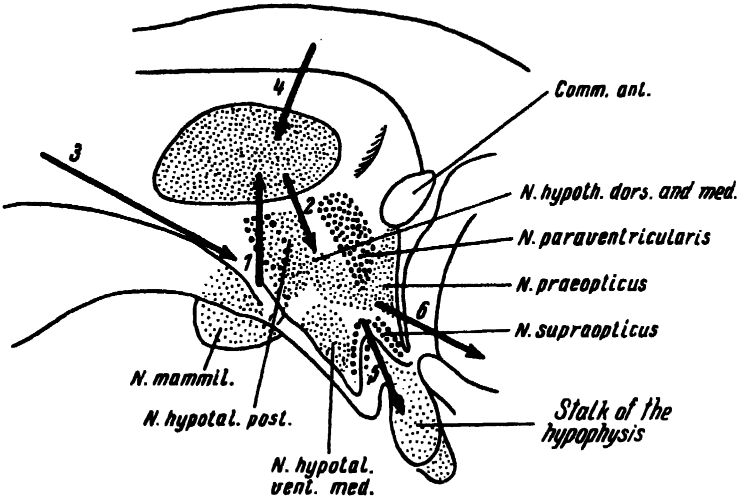


Fig. 257. Nuclei of hypothalamic region (diagram).

Arrows indicate connections of this region: *1*—ascending pathways from corpora mammillaria to optic thalamus (bundle of Vieq d'Azyr); *2*—pathways descending to hypothalamic nuclei from optic thalamus connected with cerebral cortex by fibres *(4)*; *3*—conjectural fibres extending from cerebral cortex direct to hypothalamic region; *5*—tract from supraoptic nucleus to hypophysis; *6*—fibres descending from hypothalamic region to spinal cord (tract of Karplus and Kreidl), to nuclei of the tectum and possibly, to medulla oblongata.

Fibres issuing from the supraoptic nucleus innervate the posterior lobe of the hypophysis entering it by way of the supraoptic tract which runs in the stalk of the hypophysis above the decussation of the optic nerves.

From the characteristics of the morphological connections of the hypothalamic region it follows that its nuclei may be stimulated by impulses coming both from the thalamus and the cerebral cortex. Impulses arising in the hypothalamic nuclei act upon the neurons of the vegetative nervous system. Reflex acts, involving the organs innervated by the vegetative nervous system consequently also involve the nuclei of the hypothalamic region, which is an intermediate link between the optic thalamus and the cerebral cortex, on the one hand, and the vegetative nervous system (its preganglionic neurons), on the other.

Stimulation of the hypothalamic region provokes reactions of the vegetative system. Stimulation of the posterior and lateral nuclei of the hypothalamic region produces reactions involving the sympathetic nervous system (dilation of the pupils, erection of the hair due to pilomotor contraction, increase in blood pressure, acceleration of the heart-beat, inhibition of the movements of the intestinal tract), whereas stimulation of the *tuber cinereum*—nucleus of the anterior part of the hypothalamic region—leads to effects arising during excitation of the parasympathetic neurons.

Destruction of the nuclei of the hypothalamic region deranges thermoregulation and water metabolism, since the former requires the integrity of the tuber cinereum, and the latter that of the supraoptic nucleus. Changes in carbohydrate and water metabolism were observed as a result of the destruction or stimulation of the hypothalamic nuclei.

The hypothalamic region is closely connected with the hypophysis morphologically and functionally which is particularly manifest in the regulation of water and salt metabolism. Transection of *tractus supraopticus*, the nervous pathway which connects the hypothalamic region with the posterior lobe of the hypophysis, leads to diabetes insipidus (or polyuria). Normally the conditioned and unconditioned reflexes of the kidneys, apparently, always involve the supraoptic nucleus of the hypothalamic region, whose efferent neurons innervate the hypophysis, thus regulating the secretion of the antidiuretic hormone (p. 433). Secretion of this hormone into the blood diminishes when water is introduced into the organism and increases in water deficiency.

It is possible that the nerve cells of *nucl. supraopticus* and *nucl. paraventricularis* also perform secretory functions, since they contain granules resembling those in the secretion of glandular cells. These nerve (or, as it were, nervous-glandular) cells probably secrete hormonal substances into the cerebrospinal fluid or the blood.

Some researchers assert that the hypothalamic region has special centres for fat, water, carbohydrate and salt metabolism, a centre of "sex functions," centres of heat loss and heat production, a hypothalamic centre of vascular reactions, etc. This conception is incompatible with the idea of the centres of various functions as an interconnected complex of neurons of different divisions of the brain, which are united into a centre regulating the normal course of integral complex reflex acts by the temporary connections elaborated in the cerebral cortex. The hypothalamic nuclei are not autonomous regulators of the functions of the vegetative system. The activity of these nuclei transmits to the efferent neurons of the vegetative system the impulses arising with the participation of the cerebral cortex, the thalamic and striopallidal systems in response to stimulations coming from receptors.

Theoretically it cannot be doubted that the hypothalamic nuclei do not merely transmit impulses to the vegetative neurons directly influenced by them; the activity of these nuclei must "add" something to the impulses coming to them from the higher divisions of the brain. These impulses may be extinguished in the hypothalamic region or, on the contrary, may evoke processes increasing their effectiveness. There is no experimental material on this question as yet. Nor are there any data making it possible to distinguish the influence of the impulses coming to the hypothalamus directly from the cerebral cortex from those coming from the cortex via the thalamus and the striopallidal system and those transmitted from the thalamus and the striopallidal system directly to the hypothalamic region without involving the cerebral cortex. It is only known that in infants, whose cerebral cortex is not yet fully developed, the functioning of the hypothalamic nuclei directly depends on the thalamic and striopallidal neurons. It is likewise obvious that the influences of the cerebral cortex (arising in it in response to all impulses from the receptors) continuously affect the excitability of the hypothalamic nuclei.

An important role in the development of sleep was attributed to the activity of the hypothalamic nuclei. It is true that immediate sleep can be evoked by stimulating the structures situated in the hypothalamic region with an electric current through implanted electrodes (Hess, Tonkikh). There is no reason, however, to speak of any centre of sleep (see p. 636).

The so-called emotional reactions, in which certain complexes of motor acts involve considerable changes in cardiac activity, vascular tone, properties of the blood, etc., are possible in the absence of the cerebral cortex because of the reflex activity of the system of the thalamus, the hypothalamic nuclei and the striopallidal system.

The cerebral cortex, which in complex reflex acts stimulates the vegetative neurons through the hypothalamic region, may also exert an inhibitory influence. After removal of the cerebral cortex even slight, uninjurious stimulation evokes violent defensive reflexes accompanied by marked excitation of the organs involved in these defensive reactions: the hair is erected, the pupils become dilated, the blood pressure and blood sugar increase, the blood coagulates faster. These defensive reactions, produced in decorticated cats and dogs even by uninjurious stimulations, are designated (not very happily) as "sham rage." This "sham rage" is conditioned by the intensified reflex activity of the hypothalamic nuclei, liberated from the inhibitory influences of the higher centres (W. Cannon, Bard et al.).

Some recently obtained data show that the influences, which seem continuously to inhibit the reflex activity of the hypothalamic nuclei, come from the phylogenetically oldest parts of the cerebral cortex, the so-called olfactory brain (rhinencephalon). Reflexes of "sham rage" arise in cats deprived only of the *gyrus piriformis, hippocampus, nucl. amygdalae*, and of the section of the medial cortical surface situated to the anterior of the corpus callosum with the neocortex remaining intact. Contrariwise, removal of the neocortex with the aforesaid lobes of the rhinencephalon left intact inhibits all defensive reflexes of the cats: to a pinch of the tail or fastening to the stand they react with purring and it is uncommonly hard to evoke a defensive reflex in them.

Functions of Thalamus

The thalamus together with the geniculate bodies and pulvinar are formations through which influences from all the receptor systems, except the olfactory, are transmitted to the cerebral cortex.

Functionally the region of the thalamus (Fig. 258) includes the thalamus proper with three groups of nuclei (anterior, lateral, and medial), the metathalamus with the geniculate bodies (*corpora geniculata*) and the pulvinar. Many subdivisions are distinguished in these formations; they include: a) nuclei which project fibres to the hypothalamus and to different parts of the thalamus itself; b) nuclei whose cells give off axons ascending to the cerebral cortex (fibres of conducting pathways from the spinal cord, medulla oblongata and cerebellum, i.e., fibres which transmit to the thalamus impulses running to the central nervous system along the afferent neurons come up to the cells of these nuclei); c) nuclei performing "associative" functions, i.e., nuclei which do not directly receive afferent impulses, but are connected with other nuclei of the thalamus and with the cerebral cortex.

The most important structural feature of the thalamus is that the nerve fibres of the pathways from all neurons of the spinal cord and medulla oblongata, which are in contact with the afferent fibres, terminate in its nuclei.

The ***nucl. latero-ventralis*** receives fibres from the ***nucl. ventralis*** of the cerebellum; the ***nucl. ventralis post. medialis*** receives fibres from the nuclei of the trigeminal nerve; the ***nucl. ventralis post. lateralis*** takes in fibres from the spinothalamic tract and fibres extending from Goll's and Burdach's nuclei. These nuclei of the thalamus project fibres to the cerebral cortex.

Formations known as the metathalamus functionally also relate to the nuclei of the thalamus; they include the *corp. geniculatum laterale* which receives fibres from the retina, and the *corp. geniculatum mediale* receiving fibres connected with the auditory neurons.

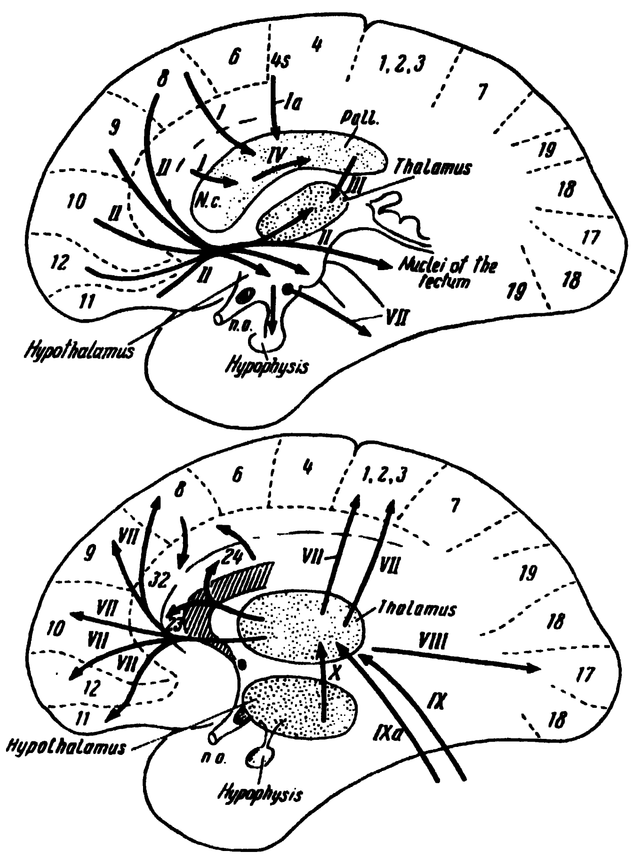


Fig. 258. Diagram showing connections of optic thalamus.

Arabic numerals indicate areas of cerebral cortex. Roman numerals indicate groups of fibres connecting different parts of brain. *Top:* scheme of fibres descending to optic thalamus from cortex, pallidal system and hypothalamic region; *I*—fibres extending to corpus caudatus *(N. c.)* from premotor zone of cortex; *Ia*—from motor zone; *IV*—fibres from corpus caudatus to globus pallidus; *III*—fibres from globus pallidus to optic thalamus; *II*—fibres from cerebral cortex to optic thalamus, hypothalamic region and nuclei of brain stem. *Bottom:* scheme of fibres entering optic thalamus and fibres emerging from it to cerebral cortex; fibres of spinothalamic tract *(IX)* and fibres *(IXa)* transmitting impulses from sensory nuclei of fifth, eighth and tenth pairs of nerves and from Goll's and Burdach's nuclei of medulla oblongata; *VIII*—fibres from lateral geniculate body to *17th* cortical area; *VII*—fibres ascending from thalamus to postcentral convolution *(1, 2, 3)* and frontal lobes of brain; *X*—fibres extending to optic thalamus from hypothalamic region; *n. o.*—nervus opticus (optic nerve).

Fibres from the nuclei of the thalamus, which form, as it were, the chief subcortical relay station for transmitting impulses from various groups of receptors to the cerebral cortex, run to different parts of the cortex, in which there is a fairly precise projection of various groups of neurons of the thalamus.

Decorticated dogs, and all the more rabbits and birds, with the thalamus intact, can perform complex coordinated acts. Birds are apparently able even to search for food; dogs are capable of coordinated reactions to painful stimulations and of executing movements of the "play" type (G. Zelyony).

Decorticated monkeys with the thalamus intact exhibit peculiar tonic reactions. The latter depend on the side on which the animal is lying (Fig. 259). The limbs of the side of the body on which the animal is lying are extended, while on the opposite side they are flexed; the hands of the latter side shows the "grasping" reflex which is important in monkeys not only for taking food, but also for climbing. This motor act is a postural reflex and arises, as shown in Fig. 259, in response to impulses from the skin (and possibly to some extent also from the muscles) caused by the contact of the monkey's body with the surface on which it is lying. In primates the coordination of this reflex act, apparently, involves the cerebral cortex.

We have already seen that the cell bodies of the peripheral afferent neurons lie in the spinal ganglia and in the ganglia of the cranial nerves. These are cells of the first afferent neuron whose axon projects one branch to the receptor and another to the spinal cord or the medulla oblongata within which they terminate at some cellular group (at the cells of the posterior horns of the spinal cord, of Goll's and Burdach's nuclei, of the vestibular nucleus, of the *tractus solitarius*, etc.). The axons of the cells, on whose surface the afferent fibres entering the brain terminate, run to the thalamus (or cerebellum). Consequently, these axons form ascending pathways extending to the thalamus (or cerebellum). The neurons, whose axons enter the optic thalamus, may be called the second afferent neurons. The cells of the thalamic nuclei give off fibres which reach different parts of the cerebral hemispheres. Thus the thalamus is, so to speak, a collector, where all the afferent impulses from the receptors of the organism (except the olfactory) converge before entering the cerebral cortex. The axons of the thalamic neurons ascending to the cerebral cortex may be called afferent neurons of the third order (Figs. 258 and 260).

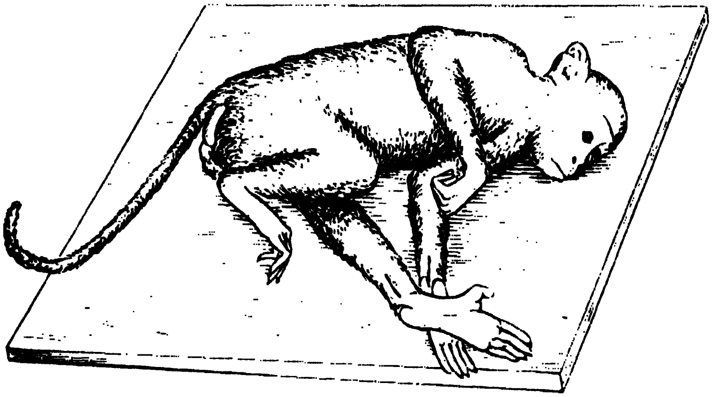


Fig. 259. Posture of decorticate monkey (with optic thalamus and part of pallidal system intact) lying on left side. When animal is laid on right side, right extremities are extended and left extremities flexed. In flexion of right hand "grasping" reflex can be clearly observed (after Fulton).

Consequently, the first afferent neuron is that whose fibre runs from the receptor to the spinal cord or medulla oblongata, its cell body lying in the spinal ganglion, or in the ganglion of the cranial nerves. The second afferent neuron is that whose cell body lies in the spinal cord or medulla oblongata and comes in contact with afferent fibres from the receptors. The axon of this second afferent neuron ends at the nerve cells of the thalamic region. The third afferent neuron is that whose cell body lies in the thalamic region and comes in contact with the axon of the second afferent neuron; the axon of the third afferent neuron ascends to the cerebral cortex. More complex connections between the cerebral cortex and the receptors are not improbable.

Each group of fibres, which conduct impulses from certain receptors, terminates at very definite points of the thalamus. The fibres which extend from the corresponding cellular groups of the thalamus to the cerebral cortex, are not evenly dispersed in the cortex, but run to more or less definite sections of the latter.

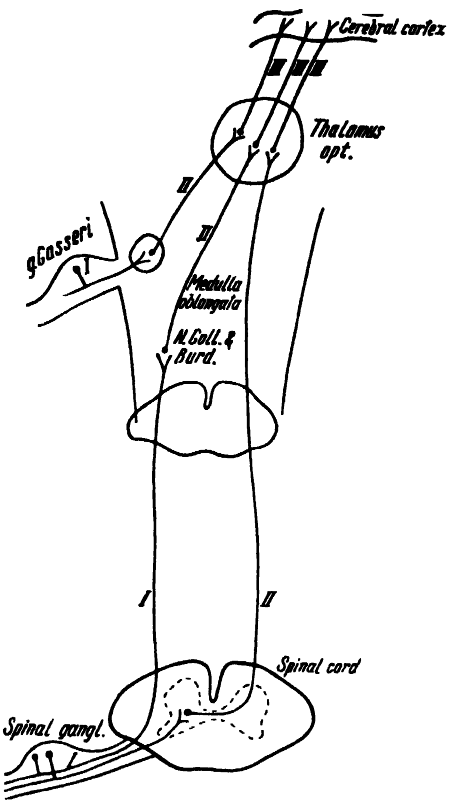


Fig. 260. Diagram of connections between optic thalamus, afferent neurons and cerebral cortex. Numerals *I*, *II* and *III* designate succession of neurons along which afferent impulses from receptors pass (endings of first neuron) to cerebral cortex.

Lesions of the thalamus entail severe disorders of reception. These lesions are sometimes accompanied by attacks of sharp pain (when the cells of the thalamus are stimulated) and by hyperpathia, but sometimes, on the contrary, by loss of sensibility.

Striopallidal System

The term "striopallidal system" (Fig. 261) covers the basal (subcortical) ganglia including the *nucleus caudatus* and the *nucleus lentiformis*. The latter consists of two parts—the *putamen* and the *globus pallidus*. The nucleus caudatus and the putamen are (phylogenetically) younger formations and are called *neostriatum*. The remaining part of the *corpus striatum* (*globus pallidus*) is designated as *palaeostriatum* (pallidum). The connections of the striopallidal system are indicated in Fig. 261.

In animals with an undeveloped cerebral cortex the striopallidal system and the thalamus form the higher division of the central nervous system.

With the development of the cerebral cortex, the functions of the striopallidal system become closely connected with the cortical processes. The striopallidal system is then regarded as part of the extrapyramidal system involved with the cerebral cortex and the nuclei of the midbrain in the coordination of complex reflex motor acts. Lesions of the nuclei of the striopallidal system are accompanied by characteristic disorders of movements.

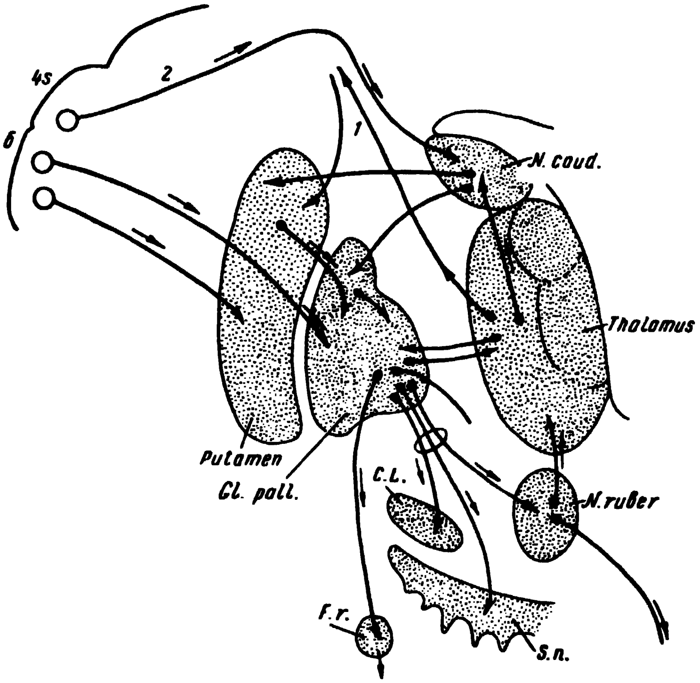


Fig. 261. Extrapyramidal system and connections of pallidal system.

6 and *4s* – areas of premotor and motor zone of cerebral cortex; *1* – fibres ascending from optic thalamus to cortex; *2* – pathway from "inhibitory sections" (p. 664) of fourth area to the nucleus caudatus *(N. caud.)*; *Gl. pall.*- globus pallidus; *C.L.* – corpus luysi; *N. ruber* – red nucleus; *S.n.* – black substance; *F.r.* – formatio reticularis of medulla oblongate. Arrows indicate direction and "destination" of impulses,

Since the functions of the striopallidal system are closely bound up with those of the cerebral cortex, mainly its premotor zone, the questions relating to this system will be considered later.

Reflexes on Different Levels of Central Nervous System

Having considered the functions of various subcortical divisions of the central nervous system, we deem it advisable to summarize the above facts and to examine the specific features of the reflex activity involving different levels of the brain.

Spinal reflexes are generally scanty with relatively few combinations in the activity of their various effectors. These reflexes are often limited by the activity of effectors innervated from the same segments of the spinal cord which receive impulses from receptors, whose stimulation evokes the given reflex. They cannot ensure any more or less complete adaptation of the organism to the changing external environment.

With the inclusion of the medulla oblongata in the reflex activity, the latter becomes much more complex. The sphere of action of the reflexes is now wider than in spinal animals.* This leads to such reflexes as vomiting, elementary reflex autoregulation of the blood pressure and respiration in response to impulses from the receptors of the aorta and the carotid bifurcation, and certain regulation of the tone of the entire motor apparatus depending on reflexes evoked from the receptors of the neck muscles and labyrinths. The influences exerted by the medulla oblongata on the entire spinal cord are manifested in these reflexes.

With the inclusion of the red nuclei of the midbrain and the phylogenetically older parts of the cerebellum in the reflex activity of the spinal cord and the medulla oblongata, new reflex acts appear, including the recovery of a definite posture (standing posture) if it is deranged; more complex respiratory activity is also in evidence.

When the diencephalon (the thalamus and the hypothalamic region) comes into play, the reflex activity of the internal organs and its integration with the motor reflexes become more complex. Such reflex acts as thermoregulation and such reactions as the so-called "sham rage" can now be effected. In the latter a number of motor reflexes (showing the claws and teeth, biting objects which stimulate the receptors of the skin on the head) are combined with reflex changes in the activity of the respiratory and cardiovascular systems, with inhibition of the movements of the intestines, increase in blood sugar, acceleration of blood coagulation, pilomotor contraction, intensification of adrenalin secretion, etc. Compared with the reflex activity of an animal with only the hindbrain and midbrain intact, that of a thalamic animal is much more varied. Finally, addition of the functions of the striopallidal system to the activity of the diencephalon makes such reflex acts as walking (experiments with beasts of prey) possible; decorticated monkeys are unable to walk (see Fig. 259).

Thus with the inclusion of ever higher levels of the central nervous system in nervous activity the reflexes become more and more complex and modified. In his last work *The System of Reflexes on Ascending Levels* A. Ukhtomsky wrote that the efferent neurons of the spinal cord and medulla oblongata were "a common executive apparatus for a series of diverse reflexes, progressively rising with the inclusion of new higher levels. Ensuring new reflex utilization of the earlier developed executive apparatus through a quantitative transformation of the conditions of its work, depending on the increasing number of receptors newly put in operation—such is, in general outline, the process..." which characterizes the reflexes on ascending levels. With the development of the higher divisions of the brain, "ever new adequate factors, to which isolated levels of the spinal cord are absolutely indifferent, now have access to the previous common executive pathway and are of stimulating significance for it" (i.e., for the terminal efferent neurons). Owing to this, "when definite reflexes and reflex arcs have already been elaborated on the lower central levels ... the higher central level proceeds in its work from these previous, beforehand given, elaborations, utilizing them in more complex reflexes already on new adequate occasions, often irrespective of stimuli from the previous receptors of the lower levels, and even in spite of them."

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* Here we, naturally, mean (as usual when considering experiments performed on spinal animals) the reflex activity of the parts of the body connected with the spinal cord below the site of its transverse section.

Consequently, the higher the level of the central nervous system, influencing the primitive reflex apparatus first of the spinal cord and then of the medulla oblongata, the more complex and diverse the interrelations between various links of the reflex acts. In the animal with a well-developed cerebral cortex, participation of the latter in the reflex activity is indispensable for the independent existence of the given individual organism, for the procurement of food and protection from noxious agents. After removal of the cerebral cortex in higher animals, however, the activity of the intact parts of the brain ensures accomplishment of a number of such inborn reflex acts as are characterized by their biological, adaptive importance for the organism. Such complex inborn unconditioned reflexes as are of biological significance for the animal as a whole, were regarded by Pavlov as instincts.

Instincts (Complex Unconditioned Reflexes)

Instincts are complex unconditioned reflexes which determine the integral adaptive acts of the organism in response to stimulations (or complexes of stimulations) of receptors.

Instincts often manifest themselves as chain reflexes in which consummation of one link of the reflex act stimulates the receptors to provoking the next link of this act. For example, in some animals definite seasonal changes in the environment act upon a number of receptors and give rise to the sex instinct which after consummation of certain of its links (for example, of various vocal and motor reactions) ends in processes leading to impregnation. Furthermore, stimulation of the interoceptors connected with pregnancy, or with the laying of eggs, in its turn often leads to a complex of different reflex acts, for example, to hatching. Similarly, birth of the young or hatching evokes new reflex acts of the parents, for example, feeding the young, etc.

Changes in the production of hormones by the endocrine glands often constitute an important link in the chain of reactions of the integral reflex act (for example, sex reflexes, the defensive reflex, hibernation). As reflex responses to stimulations of receptors, these changes in the supply of hormones to the blood, in their turn, influence the functions of various effectors.

As complex unconditioned reflexes instincts form the foundation for the conditioned reflexes. All instincts are, therefore, effected (after at least several repetitions by the given individual) as complex reflex acts, which also include conditioned reflexes.

As a result of a corticalization of functions (p. 604), a number of processes which in animals with a less developed cerebral cortex occur in the diencephalon and forebrain, in the higher mammals pass to the cerebral cortex. In higher animals certain formations of the cerebral cortex are probably required for the normal development of certain instincts, even when they are effected for the first time and have not as yet elaborated any conditioned reflexes. This is testified to, for example, by the fact that a decorticated dog does not snap at the meat which is lying before it and does not exhibit all the reactions required for the reproduction of the species. But the normal dog, even if it never before ate any meat and was for a long time fed only milk (experiments of Tsitovich, p. 621), will sniff at the meat the first time it is given some and will eat it. It follows that the alimentary unconditioned reflex is also disturbed in decorticated higher animals.

Corticalization of Functions

As the cerebral cortex develops (Fig. 262) the properties and activity of the phylogenetically older formations of the central nervous system greatly change. The more complex the structure and activity of the cerebral cortex, the more it influences the properties of all other nervous structures; the latter lose the ability to perform some of the functions which they perform when the cortex is less developed.

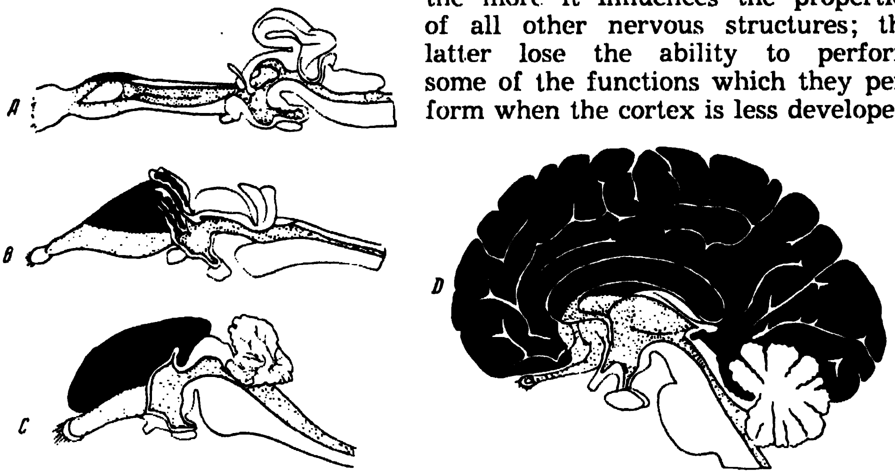

Fig. 262. Development of brain mantle.

Brain: A—of fish; B—of lizard; C—of rabbit; D—of human being (after Edinger).

This is evident, for example, from comparing the motor acts of various species of vertebrates having different lesions of the cerebral hemispheres. The frog with the cerebral hemispheres removed (amphibians have no cerebral cortex) at first sight hardly differs from the normal frog. But the dog, with completely bilaterally extirpated cerebral hemispheres and midbrain, is a totally unfit organism. It can neither move nor maintain a constant body temperature; it scarcely shows any alimentary reactions. After removal of the forebrain and diencephalon, however, dogs and cats are capable of reflex regulation of the muscle tone when changing the position of the head and body in space, and of exhibiting righting reflexes. In apes and human beings the exclusion of the cortex of the cerebral hemispheres entails a loss of the righting reflexes. Furthermore, in the lower mammals (rodents) conditioned reflexes, according to certain data, can be elaborated even in the absence of the cerebral cortex; but in dogs and, of course, in monkeys and man this is impossible.

It follows that as the cerebral cortex progressively develops it takes over—in a perfected and modified form—the functions performed more primitively by the lower divisions of the central nervous system with an undeveloped cerebral cortex. This taking over by the cerebral cortex of certain functions performed at earlier stages of phylogenetic development by the lower divisions of the central nervous system is called corticalization of functions.

C. ACTIVITY OF CEREBRAL CORTEX

CHAPTER 60

GENERAL CHARACTERISTICS OF CONDITIONED REFLEXES AND COUPLING ACTIVITY OF CEREBRAL CORTEX

Decorticated animals (we imply here higher mammals) possess only unconditioned reflexes. The number of these reflexes is relatively small, and provide for scanty reflex acts, stereotypically repeated in response to a limited number of stimuli which evoke them. But the activity of an intact organism can be balanced with the constantly changing environment only by lifelong elaboration of new reflex acts, which ensures its adaptation. These new reflex acts—conditioned reflexes—are formed in the higher mammals by the activity of the cerebral cortex. Thus, *the activity of the cerebral cortex is conditioned reflex activity.*

Elaboration of Conditioned Reflexes

Conditioned reflexes are elaborated in the course of the individual's life by formation of temporary nervous connections in the most reactive structures of the central nervous system (in higher animals it is the cerebral cortex).

The following concrete example will serve to elucidate the earlier considered mechanism by which conditioned reflexes are elaborated.

If—as already practised in Pavlov's first classical experiments devoted to the study of conditioned reflexes—we use an acoustic stimulus (for example, the beat of a metronome), or an optic stimulus (for example, the flash of an electric bulb), or any other stimulus which was never used during or before feeding the animal, this agent, stimulating the receptors of the animal, will not evoke any alimentary reaction, such as licking the lips or secretion of saliva. In this case only the orienting reflex (p. 607) will manifest itself. But if the same agent, i.e., the beat of a metronome, or the flash of an electric bulb, is used several times before feeding, the animal soon begins to react to it, just as it reacts to stimulation by food: during the action of this agent the animal turns its head in the direction from where the food is given; it begins to lick its lips and salivate. This is the result of the elaboration of an alimentary conditioned reflex.

Here is another example. A rather strong electric current is applied to the paw of a dog for one or two seconds. The dog jerks the paw away, tries to jump off the stand, whines, tosses about the stand, etc. This is an unconditioned motor defensive reflex observed in any animal when noxious stimuli act upon its receptors. No other agents, besides noxious ones, evoke this inborn reflex. But if, for example, the sound of a whistle is accompanied by the action of an electric current on the dog's paw, after several such combinations the dog will react to the sound of the whistle alone with the same defensive reflex as to the stimulation of the paw by an electric current: it will jerk the paw away, bark, toss about the stand, etc. In some cases this reaction appears very rapidly—after one or two combinations of the sound of a bell with the application of a noxious stimulus.

Conditioned stimuli, unconditioned stimuli and reinforcement of conditioned reflexes. The stimulus (agent) evoking a conditioned reflex is called a *conditioned stimulus,** while the agent evoking an unconditioned reflex is *designated as an unconditioned stimulus*. The application of an unconditioned stimulus in combination with a conditioned stimulus is called *reinforcement* of the conditioned stimulus or the conditioned reflex (sometimes it is also designated as a *combination* of a conditioned stimulus with a reinforcing agent).

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* The term "conditioned stimulus" is also applied to an agent which as a result of its first reinforcements by an unconditioned stimulus only begins to turn into an agent of a conditioned reflex, but does not yet evoke it.

Dependence of nature of conditioned reflexes on reinforcing stimulation. The reaction of effectors resulting from a conditioned reflex is *determined by the nature of the unconditioned reflex which reinforces it*. If, for example, the sound of a whistle is reinforced by feeding and not by a painful electrocutaneous stimulation the whistle will evoke an alimentary rather than a defensive conditioned reflex. But the sound of the whistle reinforced by the introduction of acid into the dog's mouth will elaborate a defensive secretory conditioned reflex to the whistle. In the first case the sound of the whistle will evoke a secretion of saliva rich in organic and poor in inorganic substances; in the second case the saliva will contain more salts than organic compounds. The sound of the whistle reinforced by introduction of water into the stomach, will cause a conditioned reflex increase in the production of urine. The sound of the whistle accompanied by inhalation of carbonic acid will lead to a respiratory conditioned reflex, intensified pulmonary ventilation; but accompanied by the action of light on the eye, it will constrict the pupil. There are as many examples as there are reactions involving the central nervous system.

The nature of the conditioned reflexes in no way depends on the stimuli by which they are evoked, or on the kind of receptors to which the stimulus has been applied; it depends solely on the unconditioned reflex reinforcing the given conditioned stimulus. This is the principal difference between conditioned and unconditioned reflexes; the nature of the latter is determined by the receptive field (different for each unconditioned reflex) from which the given unconditioned reflex has been evoked.

Possibility of elaborating conditioned reflexes to all physiological functions. Conditioned reflexes can be elaborated to any function of the organism; this was what Pavlov meant when he stated that the cerebral cortex had control over the entire organism, and when he demonstrated the possibility of elaborating conditioned reflexes to the activity of the digestive glands and skeletal muscles. Developing Pavlov's views, K. Bykov showed that all the functions of the organism depended on influences of the cerebral cortex resulting from elaboration of conditioned reflexes.

Examples illustrating the elaboration of conditioned reflexes to diverse functions of the organism were given earlier and corresponding data were presented in the discussion of all functions of the organism. It will be observed that conditioned reflexes can be elaborated to the activity of all digestive glands, to the movements of the spleen and intestines, to the work of the kidneys, to diverse changes in the activity of the cardiovascular system, respiration and endocrine glands, to changes in the composition of the blood and its various corpuscles, in the permeability of the intestinal epithelium and in the processes of general and intermediate metabolism, to any kind of muscular activity, to changes in the sensitivity of receptors, etc.

Agents transformed into conditioned stimuli. Stimulation of *any* receptor, if it is strong enough to evoke excitation in the afferent nerve fibres, can be transformed into a conditioned stimulus.

Agents of the external environment which never before evoked any noticeable reflex responses, are very often transformed into conditioned stimuli (by means of corresponding reinforcement). Such stimuli are designated as ***indifferent agents*** or indifferent stimuli. Actually, however, they are not totally indifferent, since they provoke excitation in those neurons of the central nervous system to which the excitation from the stimulated receptors is directed, and since their initial action produces the so-called orienting reflex.

Orienting reflex. Each stimulation, which previously did not affect the animal and which evokes no other unconditioned reflex, resulted in what Pavlov often called the "what-is-it?" reflex. This reflex manifests itself, for example, in the fact that the animal orientates its head and its auricles towards the source of stimulation, approaches the stimulating agent and sniffs at it.

If the stimulation evoking the orienting reflex is frequently repeated, the reflex gradually weakens and disappears. Disappearance of the orienting reflex in no way depends on the fact that the stimulus by which it is evoked has ceased to act upon the receptors and nerve centres; the effect produced by indifferent stimuli disappears because a process of inhibition develops in the cerebral cortex after repeated applications of the indifferent agent (Chapter 61). This is proved by the fact that in the dog deprived of the cerebral hemispheres the orienting reflex does not disappear, however often the stimulation is repeated.

Significance of definite correlations between time of action of conditioned and unconditioned stimuli. A definite correlation between the time of action of the conditioned stimulus and that of the unconditioned (or another conditioned) stimulus which reinforces it, is the principal prerequisite for the elaboration of a conditioned reflex (the strength of these stimuli will be dealt with on page 620). It has been found that conditioned reflexes are elaborated rapidly and become stable when the conditioned stimulus somewhat *precedes* the unconditioned stimulus. If the conditioned stimulus begins to act simultaneously with an unconditioned stimulus, or joins the latter during its action, the elaboration of conditioned reflexes is impeded, and the elaborated reflexes are easily inhibited. But if the isolated action of a conditioned stimulus lasts for a relatively long time before it is joined by the action of an unconditioned stimulus the conditioned reflex is retarded (p. 631).

The signalling property of the conditioned stimuli (p. 619) manifests itself in the fact that stable conditioned reflexes can be elaborated only when the conditioned stimulus precedes the unconditioned stimulus.

It will be observed that the question of the significance of certain correlations between the time of action of conditioned and unconditioned stimuli has been experimentally well investigated only with regard to alimentary conditioned reflexes. It is probable that these correlations will be somewhat different for other reflexes, in particular, for reflexes requiring a very long time (for example, reflex changes in metabolism under the action of different temperatures). It is possible that in some cases stable conditioned reflexes may be formed even if the conditioned stimulus acts during effectuation of the unconditioned reflex. It should also be remembered that elaboration of conditioned reflexes to time (p. 625) makes it possible to elaborate conditioned reflexes to agents, which are separated by a long interval from the moment of their reinforcement by an unconditioned reflex.

Method of Studying Conditioned Reflexes

The processes developing in the central nervous system itself in the course of each reflex act are as yet almost inaccessible to *direct* observation. The reflex activity of the central nervous system is, therefore, judged mainly by the reactions of various organs (effectors) which it determines. This requires as precise a record of the reflex reactions as possible and an accurate estimation of the stimulation of receptors which evokes these reactions.

Conditioned reflexes can be studied best when the conditioned effect is strictly delimited from the effect of the unconditioned stimulus. Furthermore, it is necessary that the function, taken as an indicator of the conditioned reflex activity, be measured and that the changes, evoked by the conditioned reflexes in the given function, rapidly disappear. It is also important that the study of the function, which serves as an indicator of the conditioned reflex activity, be easily conducted without deranging the normal state of the organism. Finally, it is highly desirable that the conditioned reflex itself and, consequently, the unconditioned reflex by which it is reinforced, be absolutely normal reflex acts of the animal. The function of the organism chosen by Pavlov for the study of conditioned reflexes, namely the secretion of the *salivary* gland, fully complied with all these requirements.

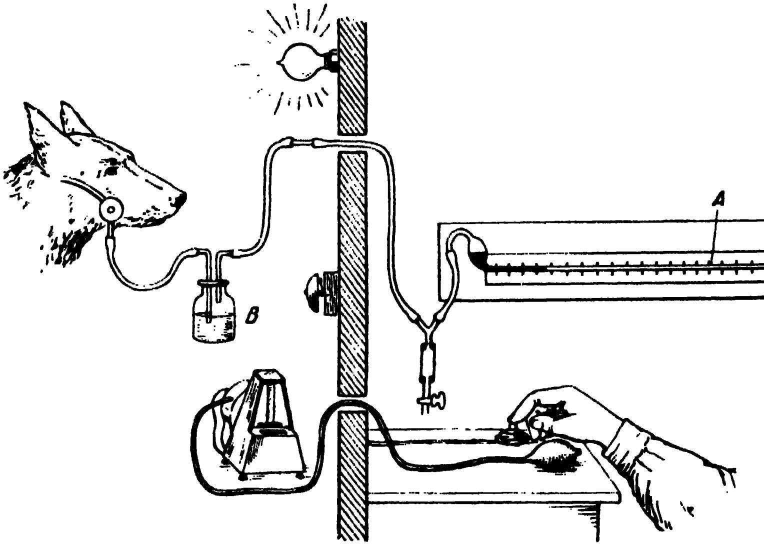

Fig. 263. Recording salivary secretion and experimenting with conditioned reflexes. Dog is separated from experimenter; without enterin mber where dog is placed experimenter ca bring into action various stimulating agents (metronome beat, sound of bell, flash of light, etc.). Diagrar shows simple set for recording secretion of saliva which moves along tube *A* fastened to scale. In tul *A* liquid is displaced by air which, in its turn, is displaced from glass *B* by saliva coming into it fro little bulb fixed at point where duct of parotid gland is brought out to surface of cheek (after N. Podk-payev, with modifica

The salivary gland was investigated by Pavlov in every detail. No other stimuli besides the nervous impulses reflexly arising from the taste receptors in response to their stimulation can normally evoke the secretion of saliva. Salivation usually stops in one to three minutes after eating. This makes it possible to carry out a series of tests of the conditioned reflex during one experiment, reinforcing it each time by an unconditioned stimulus.

In the absence of an unconditioned stimulus (i.e., without stimulation of the receptors in the oral cavity*) the secretion of each drop of saliva is due only to conditioned reflexes. *The amount of saliva secreted under isolated action of conditioned stimuli can therefore be regarded as an indicator of the intensity of the conditioned reflex.*

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* Slight unconditioned salivation in response to "painful" stimulation is also observed in dogs, who always lick the injured areas of the body.

To ascertain the values of the conditioned (and unconditioned) salivary reflexes the movement of the fluid is measured (Fig. 263) in a horizontally fixed graduated tube (manometer). This tube is hermetically connected with a bulb adjusted to the cheek of the animal where the end of the salivary duct is brought out to the exterior. Automatic graphic recording of salivary secretion is also frequently used.

To estimate the value of the conditioned reflex it is necessary to measure its intensity only during the isolated action of the conditioned stimulus, i.e., before the reinforcing unconditioned stimulus is added.

In Pavlov's laboratories the value of the conditioned salivary reflex was usually determined in 15 to 30 seconds of isolated action of the conditioned stimulus. In these experiments the animal is given food in the last second of the action of the conditioned stimulus and the action of the latter is usually not terminated immediately, i.e., not at the moment of its reinforcement by the unconditioned stimulus. Definite portions of food are most frequently used for reinforcement; it is usually dried bread powder or meat and powdered dry bread moistened with water. Sometimes instead of food reinforcement acid is introduced into the animal's mouth evoking profuse salivation, i.e., the defensive "acid" reflex. In addition to measuring the salivary conditioned reflex, the experimenter observes and records the motor reaction of the animal. The value of the unconditioned salivary reflex is also strictly ascertained.

Fig. 264. "Tower of silence," building with sound-proof chambers for studying conditioned reflexes designed by I. Pavlov and Y. Grampke (erected at Institute of Experimental Medicine in Leningrad).

As before stated, not only salivary reflexes may be used in investigating conditioned reflex activity. Various *motor* reflexes are also frequently used for this purpose. They are elaborated by the method of pain reinforcement through stimulating the skin of one of the extremities by electric current, or also by food reinforcement. In a number of cases it is expedient to investigate the vascular and other conditioned reflexes.

To study the higher nervous activity under comparatively simple conditions, it is often important to limit as much as possible the action of all stimuli on the animal, except those intentionally applied by the experimenter during the experiment. This is achieved by placing the animal in a special sound-proof chamber (Figs. 264 and 265) isolated from extraneous sounds, smells, optic stimuli, vibrations, etc.; the chamber is equipped with special apparatus allowing application of various dosed stimulations to the receptors at any time. Air or water transmission from a bulb attached to the fistula of the salivary duct (Fig. 263) enables the experimenter to record the secretion of saliva without entering the chamber. A food receptacle fixed in the stand and automatically sliding in and out makes it possible to feed the animal any time. By connecting the limbs, head, jaw, or thorax of the animal with recording levers by air or mechanical transmission it is possible to obtain records of certain motor reactions and of respiration. A special device enables the investigator to record the secretion of saliva automatically (Fig. 266).

Characteristics of Temporary Connections

Reflex arcs of conditioned reflexes. In higher animals and man formation and effectuation of conditioned reflexes necessarily involve the cerebral cortex. If the cortex of both cerebral hemispheres of the dog is completely removed, all previously acquired conditioned reflexes disappear and no new reflexes can be elaborated. The decorticated dog does not take food without assistance; it does not react to the appearance of its master, to being called by name, or to dogs of the opposite sex; in walking it stumbles on the things in its way. All this is a result of the disappearance of conditioned reflexes as represented by acts of normal behaviour. It follows that the reflex arcs of conditioned reflexes in higher animals invariably include neurons of the cerebral cortex.

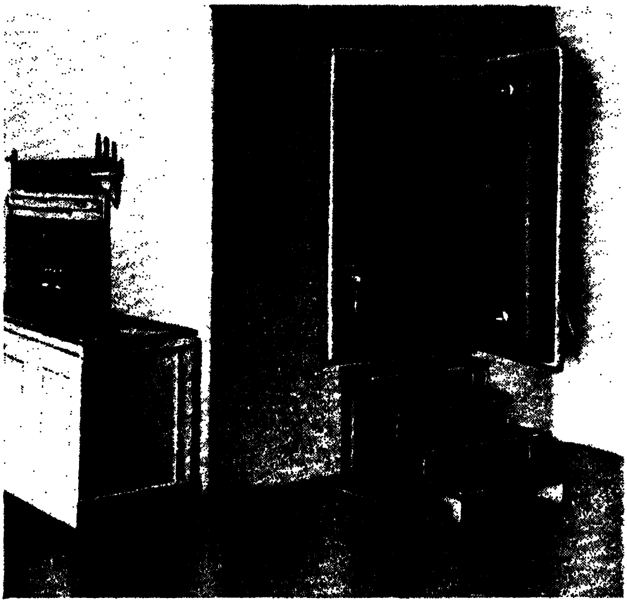

Fig. 265. Sound-proof chamber. Control panel on left.

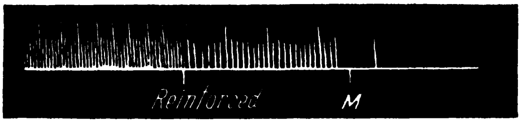

Fig. 266. Record of salivary secretion under action of conditioned (mark *M*) and unconditioned (mark *reinforced*) stimulus (read from right to left) (after N. Podkopayev).

Concept of analysers. Fig. 267 helps to understand how the reflex arcs of conditioned reflexes are formed; it shows that impulses caused by stimulation of various groups of receptors are directed to different nerve cells of the cerebral cortex. *Initially* impulses from each group of receptors evoke reactions only of definite cortical neurons which are in synaptic junction with the axons of the conductive systems that connect the cerebral cortex with the various groups of receptors. Excitation evoked by stimulation of each receptor in definite cortical cells can be transmitted to any neurons of the cortex along the pathways by which all the cells of the cortex are interconnected.

The system of nervous formations, through whose activity stimulations from the external and internal environment can evoke different reflexes, was designated by Pavlov as analysers.*

Each analyser (Fig. 267) includes, first of all, the peripheral division, i.e., the receptors, in which the energy of the stimulating agent is transformed into energy of nervous excitation. Normally, each group of receptors is excited only by a definite group of agents to which the given receptors are particularly sensitive (for example, only light or sound waves, mechanical stimulation, etc.). Furthermore, each analyser (Fig. 267) includes neurons conducting excitation from its receptors to the cerebral cortex. This is the *conductive* division of each analyser. It contains the afferent nerve fibres and nerve cells of the spinal cord, medulla oblongata and diencephalon, whose axons conduct impulses evoked by stimulation of the receptors to the cerebral cortex.

The last and higher division of each analyser is formed by the structures of the cerebral cortex. It includes all the cortical cells acted upon by the nervous impulses caused by the stimulation of the peripheral division of each analyser (i.e., receptors) and transmitted to the cortex by way of its conductive division.

Analysers are distinguished either according to the kind of receptors which constitute their peripheral division or the agent by which they are stimulated. Correspondingly, there are cortical divisions of the visual (or light), auditory (or sound) olfactory, taste, cutaneous (including tactile, pain and thermal), internal (or interoceptive), and muscular (or motor) analysers.

The action of each conditioned stimulus excites the cortical division of the analyser on whose peripheral part this stimulus acts. This takes place both when the conditioned reflex has already been elaborated, and when it is still absent, i.e., when the given agent is not yet connected with any reflex activity of the organism.

Reflex activity is possible only when impulses arising in the central nervous system in response to stimulation of the receptors are conducted to the effector organs by which this activity is accomplished. The efferent fibres directly innervating various organs of the body extend from the nerve cells situated in the medulla oblongata and the spinal cord. It follows that a conditioned reflex is elaborated when coupling in the cerebral cortex transmits excitation from the cortical cells acted upon by the conditioned stimulus to the efferent neurons, and through them to the effectors which accomplish this reflex.

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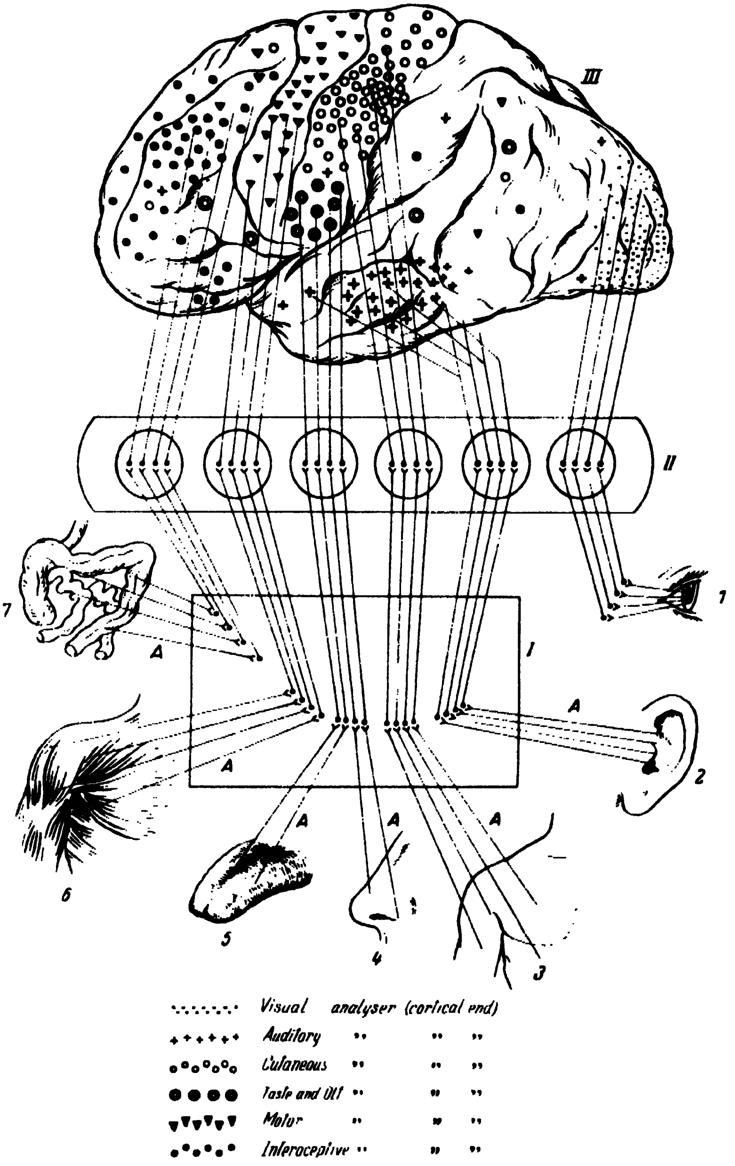
* As shown in greater detail later, the phenomena of cortical analysis are inseparably connected with the phenomena of cortical synthesis (p. 642) which develops in the same formations of the cerebral cortex. Each group of receptors roughly analyses the agents acting from the external and internal environment by its specific sensitivity to certain kinds of stimuli because of the activity of the lower divisions of the central nervous system. But higher analysis is attained only through the functions of the cerebral cortex, which contains cortical divisions of all analysers.

Cortical coupling. Elaboration of a temporary connection can be illustrated by the following example. The beats of a metronome excite certain cells of the cortical division of the auditory analyser (Fig. 268, 3). Prior to elaboration of a conditioned reflex excitation of these cells never evoked any ali-


III
II
I
1
2
3
4
5
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7
A
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A
·.·.·.·.· Visual analyser (cortical end)
+ + + + + + Auditory " " "
∘ ∘ ∘ ∘ ∘ ∘ Cutaneous " " "
● ● ● ● Taste and Olf " " "
▼ ▼ ▼ ▼ ▼ ▼ Motor " " "
• • • • • • Interoceptive " " "

Fig. 267. Diagram roughly illustrating structure of analysers.

1-7 receptors (visual, auditory, cutaneous, olfactory, taste, of motor apparatus, and of internal organs). *I* region of spinal cord or medulla oblongata receiving afferent fibres *(A)*, from which impulses are conducted to neurons situated here and forming ascending pathways; axons of latter extend to region of optic thalamus *(II)*; axons of nerve cells of optic thalamus ascend to cerebral cortex *(III)*. Disposition of nuclear parts of cortical divisions of various analysers is shown above *(III)* (with regard to interoceptive, taste and olfactory analysers this disposition has not yet been exactly established); dispersed cells of each analyser situated all over cerebral cortex are also indicated.

mentary reflexes, since it was not transmitted from the cells of the cortical division of the auditory analyser to the neurons innervating the effectors of the alimentary reflex act, i.e., salivary glands, stomach, masticatory muscles, etc. But after elaboration of an alimentary conditioned reflex to the beats of a metronome, excitation of corresponding cells of the auditory analyser evokes the same effect as direct alimentary stimulation. Consequently, elaboration of a conditioned reflex requires, according to Pavlov, coupling in the cerebral cortex of a new nervous pathway, along which excitation from the cortical cells acted upon by the conditioned stimulus, in the end, reaches the neurons innervating the organs by which the given reflex is effected.

To comprehend the mechanism of cortical coupling, it is necessary to consider in greater detail the mechanism underlying unconditioned reflexes. It is hardly doubted that the accomplishment of any unconditioned reflex is connected with excitation of certain groups of cells in the cerebral cortex* (this is testified to by the possibility of elaborating conditioned reflexes to any unconditioned reflex). Consequently, during any unconditioned reflex nervous impulses produced by stimulation of receptors invariably act on the structures of the cerebral cortex which constitute the cortical division (brain end) of the analyser from whose receptors the given reflex is evoked.

It will be observed that each unconditioned reflex, constantly repeated in the course of individual life, becomes, as it were, overgrown with a number of natural conditioned reflexes connected with it and elaborated to agents usually acting during the accomplishment of the unconditioned reflex. Unconditioned reflexes are, therefore, complex reflex acts, i.e., conditioned-unconditioned reflexes. Owing to this, when an unconditioned reflex is being effected, not only those cells of the cerebral cortex become excited, to which the impulses of the unconditioned stimulus itself are directed, but also the cortical structures which are stimulated by natural conditioned stimuli, constantly acting simultaneously with the unconditioned stimuli.

During the accomplishment of each unconditioned reflex, as has just been shown, those cells of the cerebral cortex become excited** which are acted upon by the unconditioned stimulus. If this coincides in time with the excitation of other cortical cells stimulated by the action of conditioned stimuli, the latter are coupled cortically with the cortical representation of the unconditioned reflex.

A new nervous connection arises, a new nervous pathway connecting the cortical cells which react to the conditioned stimulus with the cortical cells acted upon by unconditioned stimulation and projecting conductors to certain efferent neurons. This connection arising between cortical cells acted upon by conditioned and unconditioned stimulation because of their coincidence in time is called *temporary cortical connection*. Fig. 268 presents a scheme in which the temporary cortical connection is conventionally designated by an arrow joining the cortical cells of the auditory analyser excited by the sounds of a metronome (conditioned stimulus) with the cortical cells of the taste analyser stimulated by the action of gustatory substances evoking an unconditioned reflex.

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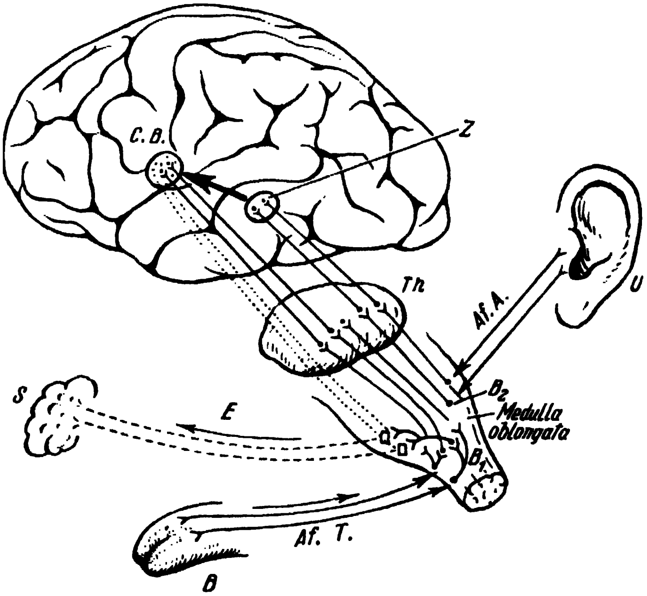
* In man and some animals formation of various structures of the cerebral cortex does not end with the moment of birth. The role of the higher division of the central nervous system at this period is partly played by the striopallidal nuclei and thalamus. It has not been proved, however, that in newborn children the cerebral cortex does not function at all at the time of birth and does not play any role in the accomplishment of unconditioned reflexes and elaboration of conditioned reflexes.

** The cerebral cortex may also respond with inhibition (p. 629) to the impulses from receptors, whose stimulation evokes unconditioned (and conditioned) reflexes.

It can be generally said that temporary connections arise between groups of neurons of the cerebral cortex whose stimulation coincides in time. Such connections are established when excitation of any cells of the cerebral cortex evoked by stimulation of any receptors coincides in time with some unconditioned reflex or a previously elaborated conditioned reflex.

Mechanism of elaboration of temporary connections and significance of irradiation of excitation in cerebral cortex. What is, then, the mechanism underlying elaboration of a temporary nervous connection between groups



g. 268. Simplified scheme illustrating mechanism of elaboration of salivary alimentary conditioned reflex to sound stimulus.

B → *Af.T.* → *B_1* → *E* → *S* — reflex arc of unconditioned salivary reflex; *C.B.* — cortical representation of alimentary unconditioned reflex (mainly, cortical division of taste analyser); *Z*—cortical division of auditory analyser; *U* → *Af.A.* → *B_2* → *Z* → *C.B.* → *E* → *S* reflex arc of conditioned reflex. Heavy arrow indicates coupling of temporary connection in cortex. *B*—receptor of taste stimuli; *U*—receptor of auditory stimuli; *B_1*—cells of medulla oblongata receiving taste stimuli and transferring them to efferent neurons or salivary gland; *B_2*—cells of medulla oblongata receiving auditory stimuli which, like taste stimuli, are conducted further to cortex; *Th*—optic thalamus, where all impulses arising in medulla oblongata during stimulation of taste and auditory receptors are transferred to neurons giving off fibres to cerebral cortex. Dotted lines indicate pathways along which impulses from cortex are conducted to efferent neurons forming efferent fibres to salivary gland *S*; *E*—efferent fibres to gland; *Af.T.* and *Af.A.*—afferent fibres from taste and auditory receptors.

of cortical cells acted upon by a conditioned stimulus and the cortical cells stimulated during the accomplishment of an unconditioned reflex? (For the sake of brevity, the term "cortical centres" of conditioned and unconditioned reflexes in the cerebral cortex is sometimes used.)

We are already familiar with the phenomenon of irradiation of excitation (Chapter 52) in the central nervous system. It has already been pointed out that a certain degree of this irradiation in the form of propagation of impulses from one neuron to another is a requisite for reflex activity. Of course, irradiation of excitation also occurs from the cortical centre of the conditioned reflex, otherwise excitation of the cortical cells stimulated by the action of the conditioned stimulus could not evoke excitation in the cortical cells of the centre of the unconditioned reflex. But if a stimulus evoking only an orienting reflex acts upon the organism alone, while the entire cortex is in a state of relative rest, this orienting reflex usually soon disappears.

Excitation from cortical cells acted upon by indifferent stimuli does not irradiate in a definite direction and is, as it were, extinguished without evoking any excitation in other structures of the cerebral cortex.

The picture changes, if excitation of one group of cortical cells coincides in time (in typical cases somewhat preceding it) with excitation of another group of cortical cells excited in the presence of a certain unconditioned (or previously elaborated conditioned) reflex. After more or less frequently repeated simultaneous excitation of these centres, impulses from the centre of the conditioned reflex irradiate in the direction of the cortical centre of the reflex by which it was reinforced, and upon reaching it, excite it.

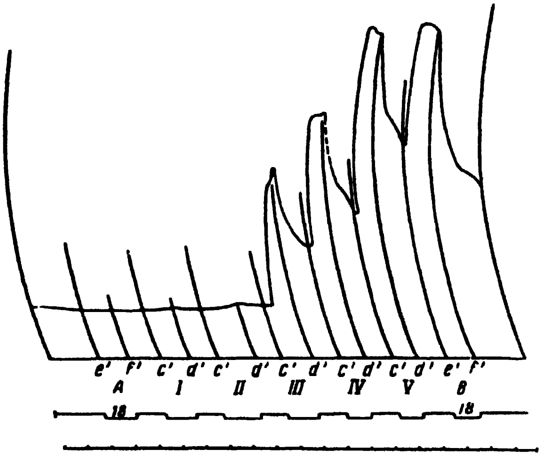


Fig. 269. Record of movements of monkey's hand (macaco) during flexion produced by stimulation of motor zone of cerebral cortex.

Upper curve: arched lines e', f', and c', d' denote beginning and end of seven successive stimulations of two points of cortical motor zone by electric current of same intensity. First stimulation of first point *(A)* did not produce any effect, i.e., was subthreshold. Next five stimulations *(I, II, III, IV,* and *V)* of another point, situated 4 mm. from first point, produced "primary facilitation," i.e., gradual emergence and intensification of contraction of flexor muscle. Second, also subthreshold stimulation of first point *(B)* now produces strong effect. This is "secondary facilitation" (after Graham-Brown).

Pavlov wrote: "...it must be admitted as a general phenomenon in the higher division of the central nervous system that any strongly stimulated centre somehow attracts to itself any other weaker stimulation simultaneously getting into this system...."* In another work Pavlov stated that when the coincidence in the time of action "...of indifferent stimuli with our active centre repeats many times, the indifferent stimuli, instead of irradiating over the cerebral hemispheres, as would be the case if they were not attracted, establish for themselves a permanent narrow pathway to the active centre, become connected with it and thus turn into definite stimuli of this centre."**

Discussing the mechanism by which the reflex arc of a conditioned reflex is coupled, Pavlov pointed out that "... there are facts which permit us to regard the act of coupling even as an elementary physiological process."*** He often stated that the "attraction" of excitation from the cortical centre of a conditioned reflex by a strongly excited cortical centre of an unconditioned reflex resembles the phenomena of blazing new paths, i.e., "Bahnung," or "facilitation." In these phenomena the effect of excitation of one

* I. Pavlov, *Complete Works*, Vol. III, Book 2, p. 110.
** *Ibid.*, Book 1, pp. 198-99.
*** *Ibid.*, Book 2, p. 52.

centre is intensified by simultaneous stimulation of another centre. This is why, for example, the knee-jerk is intensified when the fist is clenched. The following fact also belongs to the foregoing phenomena: stimulation by an induction current applied to the so-called motor zone of the cerebral cortex and not provoking any motor effect by itself, greatly intensifies the motor effect produced by simultaneous stimulation of another section of the same zone (Fig. 269).

The ability of the excited centre (dominant, see p. 575) to intensify its excitation at the expense of excitation of other centres is also observed in the lower parts of the central nervous system. There is a profound difference, however, between the elaboration of a temporary connection which ensures formation of a conditioned reflex and the phenomena of "facilitation" and dominant: with these phenomena the two groups of simultaneously excited neurons generally interact only during stimulation of these nervous structures from corresponding receptors. Whatever the frequency of simultaneous excitation of centres *A* and *B* in the lower divisions of the central nervous system, isolated stimulation of centre *A* does not acquire the ability of producing the excitatory effect in centre *B*.* But after elaboration of a conditioned reflex the cortical centres of the conditioned (*A*) and unconditioned (*B*) reflexes are in such a relation that excitation of centre *A* produces the excitatory effect in centre *B* without (or prior to) its direct stimulation. Elaboration of the conditioned reflex is most clearly manifested precisely in this effect produced by an isolated application of a conditioned stimulus. Saliva is secreted at the sound of a bell which was earlier repeatedly accompanied by feeding and it flows during the isolated action of the bell at a time when the dog has no food in its mouth.

Formation of a temporary connection between the cortical centres of conditioned and unconditioned reflexes depends on properties of the higher division of the nervous system which its lower formations do not have: the cortical cells can sometimes retain indefinitely (all through life) traces of the process which occurred in the cerebral cortex when the irradiating excitations met. This retention of the well-beaten pathway between the centres of the conditioned and unconditioned reflexes in the cerebral cortex is the distinguishing feature of the temporary nervous connections which constitute the cortical mechanism of conditioned reflexes. The physicochemical processes developing in the cerebral cortex at the time are still unknown.

Some foreign researchers endeavoured to prove it was possible to elaborate "spinal conditioned reflexes" and that elaboration of temporary connections was not a mechanism characterizing higher nervous activity. E. Asratyan's experimental studies showed these assertions to be groundless. It does not follow, however, that conditioned reflexes can be studied isolately from the more primitive forms of nervous activity merely because they characterize the activity of the cerebral cortex. Without knowing the lower mechanisms of the reflex activity it is impossible to comprehend the specific features of its higher mechanisms (as it is impossible to understand the transmission of impulses through a most elementary reflex arc without knowing the mechanisms by which a nervous impulse spreads along a nerve fibre).

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* It cannot be said that there are no trace reactions in the activity of the lower centres at all. Under the term inertia of the dominant Ukhtomsky described the ability of an excited centre to divert upon itself impulses from other reflex arcs of the spinal cord within a certain period of time after suspension of the stimulation which produced the dominant. But these trace reactions in the lower parts of the central nervous system cannot lead to elaboration of any new acts of behaviour. Phenomena of inertia of the dominant in the activity of the lower centres are extinguished in a relatively short space of time (probably in several hours).

In describing the conditioned reflex, Pavlov not infrequently used the terms "temporary connection" and "conditioned reflex" as equivalents. He wrote: "*. . . the permanent connection between the external agent and the response of the organism, which evokes it, can be rightly called an unconditioned reflex and the temporary connection—a conditioned reflex.*"* (1935.)

The term "temporary connection" in no way implies, however, that the mechanism of this connection itself dooms the latter to disappearance and that this connection can, therefore, exist only a limited time. Pavlov always emphasized the dependence of the temporary connections on the conditions of their elaboration. When a conditioned reflex has been elaborated, it is no less stable than an unconditioned reflex, as long as the conditions of its elaboration persist, i.e., reinforcement by an unconditioned reflex. If a conditioned reflex has been elaborated to a certain stimulus, it does not disappear, unless it is specially extinguished (i.e., if the action of the conditioned stimulus is not reinforced); sometimes it persists unused for many years (or recovers after one or two reinforcements). "Recognition" by the dog of its former master after many years of separation, or retention in our memory till old age of the features of people we saw only in childhood, are ensured by the same cortical mechanism—the persistence in the cerebral cortex of the once elaborated temporary connections.

Conditioned Reflexes and Their Age Development in Various Animals

Conditioned reflexes are observed in most diverse representatives of the animal kingdom.

Animals which do not have cerebral hemispheres develop and effect conditioned reflexes by the activity of the older structures of the central nervous system. It is possible that in amphibians and fish primitive conditioned reflexes are formed by the activity of the diencephalon and midbrain. The possibility of elaborating conditioned reflexes in lower Chordata (ascidians) has also been demonstrated (E. Kreps). Conditioned reflexes can be likewise elaborated in invertebrates (for example, in Arthropoda), probably, mainly by the central formations connected with the higher receptors—the ganglia of the anterior divisions of their bodies.

Investigations of the Institute of Experimental Medicine have demonstrated that conditioned reflexes can be elaborated in puppies and children and even in prematurely born children already in the first days of their life. Thorough researches carried out by N. Kasatkin have established a number of features characterizing the gradually growing complexity of conditioned reflex activity in early childhood.

Primary Generalization of Conditioned Reflexes

When a conditioned reflex to a certain agent is already elaborated, it turns out that several similar agents always evoke the same conditioned reflex, although their action has not been reinforced by an unconditioned stimulus. It follows that a temporary connection with the cortical cells of the unconditioned reflex is established not only by the cortical cells acted upon by the conditioned stimulus reinforced by the unconditioned reflex, but also by other cortical neurons. For example, if the tone of 1,000 cycles per second is accompanied several times by the introduction of acid into the mouth the salivary defensive ("acid") reflex will also manifest itself in response to tones of 100 and 10,000 cycles per second and sometimes even to any acoustic stimuli in general. This phenomenon is called generalization of conditioned reflexes.

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* I. Pavlov, *Complete Works*, Vol. III, Book 2, p. 324.

Generalization of conditioned reflexes does not usually extend beyond the analyser on which the conditioned stimulus acts. For example, after elaboration of a conditioned reflex to a certain acoustic stimulus, this conditioned reflex is at first evoked by any more or less similar sounds, but not by an optic stimulus. But in trace conditioned reflexes, i.e., when from one to three minutes elapse between the end of the action of the conditioned stimulus and the beginning of the action of the unconditioned stimulus, generalization is so extensive that almost any stimulus evokes the same conditioned reflex which is elaborated when only one definite agent is reinforced by the unconditioned reflex.

The mechanism of generalization was described by Pavlov as follows: "If a special chosen agent is brought into connection with some physiological activity for the first time, the excitation produced by this agent, on reaching a certain point of the cerebral cortex, irradiates over the given receptive centre; thus, it is not one point of the brain end of the given analyser that makes a definite connection, but the entire analyser, or some part of it; only later, owing to the opposition of the inhibitory process, the sphere of excitation gradually narrows and the result is an isolated action."* Primary generalization of conditioned reflexes is thus due to the fact that excitation, coming from receptors to definite cortical cells, irradiates from the latter over the cerebral cortex. Generalization of conditioned reflexes like that of spinal reflexes (p. 574), consequently, results from irradiation of excitation; generalization of conditioned reflexes is overwhelmed and suppressed by cortical inhibition (see below).

Two-Way Temporary Cortical Connections

Two-way connections are formed between the cortical centres of a conditioned and an unconditioned reflex. "... When two nervous centres are connected or linked," Pavlov wrote, "the nervous processes move from one to the other in both directions."**

This conclusion was based on the following experiments (N. Krasnogorsky). If passive flexion of the dog's leg (accomplished by the experimenter) is accompanied by feeding, stimulation of the receptors of the muscles is transformed into a conditioned stimulus of the alimentary reflex: flexion of the leg evokes an alimentary reaction—secretion of saliva. After elaboration of this reflex the dog, when receiving food, begins to move its leg. Thus, excitation travels not only from the kinesthetic cortical cells, i.e., cortical cells receiving impulses from the receptors of the muscles, to the cells of the cortical representation of the food centre, but also in the opposite direction; arising in the cortical division of the food centre, it runs to the cells of the motor analyser (kinesthetic cells), which conditions the movements of the extremities.

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* *Ibid.*, Book 1, p. 181.

** *Ibid.*, Book 2, p. 185.

A number of phenomena, constantly observed by us on ourselves, are due to formation of two-way connections in the cerebral cortex. Many people know that while the smell of palatable food evokes alimentary excitation, a hungry man may, contrariwise, be haunted by various food odours, by visual images of favourite dishes, etc. Signals of stimulation by cold cause contraction of cutaneous blood vessels, trembling and heightened metabolism, while excitation of the mechanisms of thermoregulation (increased heat production, diminished heat loss), without any actual influence of cooling (for example, in fever), contrariwise, produces a sensation of chilling.

Two-way cortical connections are very important in the formation of a number of natural conditioned reflexes which determine normal activity of the internal organs and coordination of various processes in the organism. It is a well-known fact, for example, that contraction of an empty stomach evokes alimentary excitation. This is most naturally accounted for by the fact that peristaltic movements of the stomach increase in the act of eating; when similar movements arise outside the act of eating, with a hungry composition of the blood, impulses from the gastric (probably, also intestinal and glandular) interoceptors, lead to excitation of the food centre by virtue of the two-way character of the cortical connections. Here is another example: stimuli, frequently coinciding in time with the state of fatigue, produce this state even without any preceding long-continued work and this is manifested, in particular, in changed respiration. Suffice it, however, experimentally to produce the same change in respiration that occurs in hard work, to reduce efficiency.

The physiological mechanism of the two-way cortical connections makes it, therefore, possible to explain the formation of such behaviour acts as do not simply reproduce unconditioned reflexes (for example, after elaboration of an alimentary conditioned reflex in the dog; when told to give the paw the hungry dog produces this movement, i.e., lifts its paw, even without the action of this conditioned sound stimulus).

Conditioned Reflexes as Reactions to Signalling Stimuli

Owing to the elaboration of conditioned reflexes, the organism meets the action of the unconditioned stimulus, preceded by the conditioned stimulus, when all reactions, which ensure equilibration of the organism with the factors evoking the given unconditioned reflex, are already in evidence. For example, when food gets into the oral cavity, it encounters saliva which was secreted by the conditioned alimentary reflex; muscular activity begins when the conditioned reflexes elaborated to it have already evoked increased respiration and heart rate, redistribution of the blood and changes in the vascular system.

But the significance of conditioned reflexes is not confined to the fact that owing to them physiological changes in each system of the organism precede the action of the agents which are their inborn stimulators. This is proved by the experiment on the dog in which the cerebral hemispheres have been extirpated. "In addition to the internal reflexes such a dog retains the fundamental external reflexes. It is attracted by food; it keeps away from destructive stimuli.... And still it is an invalid and cannot exist without care. Evidently something vital is missing in its nervous activity. But what? It is impossible not to see that the number of stimulating agents evoking reflexes in this dog has decreased considerably, that the stimuli act at a very short distance and are very elementary, very general and undifferentiated. Hence, the equilibrium of this higher organism with the environment in a wide sphere of its life has also become very elementary, limited and obviously inadequate."* "The environment of the animal is so infinitely complex and so continuously in a state of flux, that the intricate and complete system of the organism can become equilibrated with the environment only if it is also in a corresponding state of constant flux."**

Thus, "... the fundamental and most general activity of the cerebral hemispheres is signalling, the number of signals being infinite and the signalization variable."*** As a result of conditioned reflex activity, there arise new acts of behaviour, without which the activity of each organism would be limited to a small number of inborn reactions.

Related to the signalling significance of the conditioned stimuli is the fact that formation of conditioned reflexes is easiest and quickest when the conditioned stimulus directly precedes the unconditioned stimulus and subsequently acts for some time simultaneously with it. If the conditioned stimulus is applied only after the unconditioned stimulus and is suspended before the end of the latter, the conditioned reflexes are formed with difficulty (A. Krestovnikov); they are unstable and susceptible to inhibition (about the mechanism of this phenomenon see below).

Significance of Strength of Conditioned and Unconditioned Stimuli

The elaboration and strength of a conditioned reflex are determined by the intensity of the conditioned stimulus and the unconditioned stimulus which reinforces it. Of prime importance in this respect is the strength of the provoked excitation rather than the physical intensity of the stimulus, while the intensity of excitation produced by a stimulus depends on the biological role of the latter, on the state of the animal, and on the conditions under which the given agent acts.

As a rule, a conditioned reflex is formed when the conditioned stimulus is weaker (that is, when it evokes weaker excitation in the cortex) than the unconditioned stimulus by which it is reinforced. In other words, when a temporary cortical connection is elaborated, the focus of stronger excitation in the cortical centre of the reinforcing (unconditioned) stimulus usually "attracts" the excitatory process from the weaker focus of excitation, which in the given case is the cortical centre of the conditioned reflex. It is difficult, for example, to elaborate an alimentary conditioned reflex in the dog, well fed before each experiment. On the contrary, by intensifying the alimentary excitability by fasting, it is possible to transform even a noxious agent, which usually evokes the defensive reflex, into an alimentary conditioned stimulus.

All other things being equal (i.e., the strength of the unconditioned reflex being the same), conditioned reflexes to weak stimuli are formed with greater difficulty than to stronger stimuli.

When a conditioned reflex is already elaborated, its strength (for example, the amount of saliva secreted in an alimentary conditioned reflex) is subject to a relation which is designated as the "law of force." This relation consists in the fact that a conditioned reflex—all other things being equal—is the stronger, the greater (within a certain limit) the physical strength of the conditioned stimulus. But each stimulus has its "strength limit," beyond which any further strengthening of the stimulus no longer increases the intensity of the conditioned reflex evoked by it, but, on the contrary, reduces it. This is due to the fact that the cerebral cortex reacts to a supramaximal stimulus with development of inhibition (transmarginal inhibition, p. 629). The strength of the stimulus, an excess of which results in the development of transmarginal inhibition, varies with the type of nervous system and its functional state (consequently, the state of the organism as a whole).

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* *Ibid.*, Vol. IV, pp. 28-29.

** *Ibid.*, p. 30.

*** *Ibid.*

The strength of conditioned reflexes depends not only on the strength of the conditioned stimuli, but also on the strength of the reinforcing unconditioned stimuli. It has been found that strengthening of an unconditioned stimulus (and thereby of the unconditioned reflex) leads to intensification of the conditioned reflex which is reinforced by it.

When unconditioned reflexes are very strong the weakest stimulus may sometimes evoke a very intense reaction. In man intense respiratory, cardiovascular and motor reactions may emerge in response to a whispered word (stimulus of the second signalling system). But here, too—all other things being equal and with the same reinforcing stimulus—the strength of the complex reflex act depends on the intensity of the conditioned stimulus.

Natural and Artificial Conditioned Reflexes

Natural conditioned reflexes are conditioned reflexes to agents which normally act jointly with stimuli that evoke unconditioned reflexes.

For example, an alimentary conditioned reflex to the smell of meat is a typical natural conditioned reflex. The following experiment performed by I. Tsitovich proves that this is really a conditioned, i.e., elaborated reflex. Tsitovich fed a number of puppies milk. When the puppies grew up, he made them a salivary fistula; after the animals had become accustomed to the conditions of experimentation aimed at recording the secretion of saliva, he tested the action of meat on them. It turned out that in the dogs, which had never before eaten any meat, the sight and smell of meat evoked a strong orienting reaction unaccompanied by salivation; the puppies raised exclusively on milk showed no conditioned reflex salivation to the sight and smell of meat. But after the puppies had been fed meat once or twice, the sight and smell of it sufficed to evoke in them the characteristic alimentary conditioned reflex with its motor and secretory (salivation) components.

Another illustration of a natural conditioned reflex is the heightened metabolism observed in a man who only watches the performance of muscular work to which he is accustomed. All the conditions of habitual work should, therefore, be regarded as a natural conditioned stimulus for people who perform this kind of work.

There is not a single unconditioned reflex not "overgrown" with natural conditioned reflexes, since there are actually no reflexes which are normally evoked only by one agent free from invariably concomitant stimuli. The peculiar features, which characterize the physiological reactions of various species of animals, largely depend on natural conditioned reflexes connected with the accomplishment of these reactions. Therefore, when we speak about reinforcement of conditioned reflexes by unconditioned reflexes, about establishment of connections between cortical structures reacting to conditioned and unconditioned stimuli, the term "unconditioned reflex" is used by us without any additions, but for the sake of brevity. Actually, however, an unconditioned reflex is almost always (except the period of infancy, i.e., before the conditioned reflexes are elaborated) not only and not merely an unconditioned reflex. It is a complex reflex act which, as an integral whole, includes natural conditioned reflexes to a number of stimuli, normally connected with the accomplishment of the given act. When new conditioned reflexes are elaborated to an already existing complex reflex act, the sphere of its action is extended, and it can be modified by forming conditioned reflex connections with other complex reflex acts.

Natural conditioned reflexes are less susceptible to inhibition than artificial reflexes; they are more easily restored after various pathological influences (partial removal of the cerebral cortex, intoxication) which lead to temporary disappearance of conditioned reflexes.

Artificial conditioned reflexes are such conditioned reflexes which are intentionally elaborated to agents, normally never connected with the action of an unconditioned stimulus. Artificial conditioned reflexes should not be contrasted with natural reflexes.

Characteristics of Various Conditioned Reflexes Depending on Stimuli by Which They Are Evoked

Exteroceptive conditioned reflexes. Any stimulation from the external environment, if it excites the exteroceptors, may lead to the formation of a conditioned reflex after its repeated reinforcement by a stimulus which evokes an unconditioned reflex. Hence, conditioned reflexes are elaborated to various auditory, olfactory, taste, visual, mechanical and thermal stimuli.

The number of reinforcements of the conditioned stimulus by an unconditioned stimulus, necessary to elaborate a stable conditioned reflex, greatly varies with the type of nervous system and the strength both of the unconditioned and conditioned stimuli. The stronger these stimuli, all other things being equal (if their intensity does not exceed the strength limit), the fewer combinations are required to elaborate the conditioned reflex. To elaborate a conditioned reflex to the stimulation of exteroceptors in the dog usually requires 5 to 20 combinations with the unconditioned stimulus. To elaborate a natural conditioned reflex, which was always also elaborated in the ancestors of each individual of the given species (for example, an alimentary conditioned reflex to the smell of food) even two or three combinations are often sufficient. Defensive conditioned reflexes are likewise elaborated very quickly—after one or two combinations with a strong noxious stimulus.

At first the conditioned reflexes are unstable after their elaboration, i.e., their action ceases if for a certain period of time they are not exercised. After repeated reproduction and reinforcement, the conditioned reflexes become fixed and do not disappear even if not acted upon by the given conditioned stimulus for a long time.

Conditioned reflexes to stimulation of interoceptors of musculature. In Pavlov's laboratory N. Krasnogorsky found that conditioned reflexes could be elaborated by reinforcing the passive flexion of an extremity with an alimentary or defensive unconditioned reflex. It has been shown that in this case formation of conditioned reflexes depends on stimulation of the receptors of the skeletal muscles, tendons and ligaments, i.e., broadly speaking, on the interoceptors of the organs of movement. These conditioned reflexes from receptors stimulated during various motor acts play a very important part in the coordination of movements (Chapter 54) and in the formation of speech (Chapter 73).

Conditioned stimuli from interoceptors of internal organs. As was assumed by Pavlov and proved by the experiments of Bykov and his collaborators, conditioned reflexes could be elaborated to stimulation of the interoceptors of internal organs. For example, by combining the inflation of a balloon, inserted into the stomach, with feeding, it is possible to obtain an alimentary conditioned reflex to the stimulation of the mechanoreceptors of the stomach. Similarly, by introducing water into the stomach through a fistular tube (heated, for example, to 18° C) and by combining this interoceptive stimulation with an electric stimulation of the paw it was found possible to elaborate a typical defensive conditioned reflex (Fig. 270) to the introduction of water with the aforesaid temperature into the stomach. If the introduction of water having a different temperature (5°) into the stomach is not reinforced by an electrocutaneous stimulation, a differentiation (p. 630) is elaborated to the nonreinforced stimulation of the gastric thermoreceptors (Fig. 270).

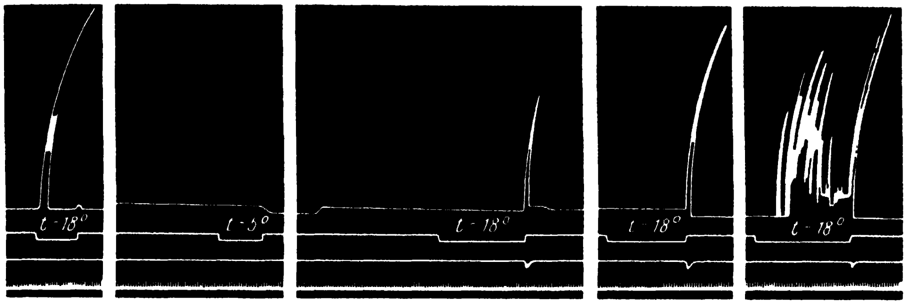

Fig. 270. Example of elaboration of conditioned reflex and differentiation to interoceptive conditioned stimulus by introduction of water into stomach through fistula.

Introduction of water (18°) into stomach was repeatedly reinforced by electrocutaneous stimulation of left paw, owing to which after elaboration of conditioned reflex isolated application of conditioned stimulus produced defensive conditioned reflex - jerking back of paw. Introduction into stomach of water having temperature of 5° was not reinforced by electrocutaneous stimulus and, therefore, did not produce any defensive reaction (differentiation).

Use of differentiation shows successive inhibition.

Top to bottom: record of movements of left paw, mark of conditioned stimulation and mark of unconditioned stimulation. Time interval —one second (after K. Bykov).

It is also possible to elaborate alimentary and defensive conditioned reflexes to stimulation of the receptors of the uterus by acting upon its mucous membrane in a chronic experiment through a fistula fixed in the cornu of the uterus. Conditioned reflexes (alimentary, defensive, respiratory, thermoregulatory, and others) were also obtained by stimulating the thermoreceptors of the stomach, the receptors of the intestinal mucosa, and the chemoreceptors of the lungs and large blood vessels (in the latter case inhalation of air with carbon dioxide served as an unconditioned stimulus in corresponding experiments).

Elaboration of conditioned reflexes from interoceptors usually requires more reinforcements than that from exteroceptors. Many variations are possible here, but elaboration of stable reflexes to stimulation of the interoceptors of internal organs requires an average of 30 to 60 reinforcements with the unconditioned reflex. At the same time interoceptive reflexes are inhibited with greater difficulty than exteroceptive reflexes.

Complex conditioned stimuli. Normally conditioned reflexes are most frequently elaborated to agents which simultaneously or consecutively stimulate several groups of heterogeneous receptors. Such conditioned reflexes elaborated to simultaneous (or consecutive) stimulation of heterogeneous receptors are called conditioned reflexes to a complex stimulus, or complex conditioned reflexes (details may be found on p. 645).

Elaboration of conditioned reflexes to agents evoking unconditioned reflexes. An unconditioned stimulus can also be utilized as a conditioned stimulus, which is illustrated by the following experiment performed in Pavlov's laboratory.

An electric current from an induction coil was applied to the skin of the dog. The current was of such intensity that the dog displayed an obvious defensive reaction: it whined, tried to jump off the stand, etc. After 5 seconds of such isolated stimulation by the electric current the dog was given meat; prior to each experiment the dog had not been fed for a long time (about 24 hours) and was therefore in a state of marked alimentary excitation. After several combinations of the noxious stimulation with the act of eating stimulation of the skin by electric current turned from an unconditioned stimulus of the defensive reflex into a conditioned stimulus of the alimentary reflex. As a result, in response to painful stimulation by electric current the dog began to lick its lips, salivated and turned in the direction from which the food receptacle usually appeared.

The picture changed, however, when the noxious stimulation was considerably intensified by application of electrodes to the area of the skin directly over the bone. With such intensified action of the noxious stimulus, excitation in the cortical centre of the defensive reflex could no longer be attracted by the simultaneously excited food centre, but, on the contrary, itself began to attract the excitation evoked by the alimentary stimulus. Intensified electric stimulation of the skin therefore not only produced a violent defensive reaction, but the latter began to emerge at the sight of meat alone, without any electric stimulation of the skin. It was not the "pain" agent which then became a conditioned stimulus of the alimentary reflex, but, on the contrary, the alimentary excitation which turned into a conditioned stimulus of the defensive reflex. In this case the significance of the intensity of excitation in simultaneously excited centres of the cortex, as a factor determining the direction in which excitation moves according to the temporary connection established in the cortex, is very clear.

The biological significance of these relations is obvious: dogs, especially wild dogs, must often procure their food literally in battle; should painful stimulations of the skin always suppress the alimentary reflex, the animal would die of hunger. But when the accomplishment of the alimentary reflex threatens the safety of the animal's skeleton, then in order to survive it is more important for the animal to avert the given pernicious stimulus than to go on procuring food.

The possibility of transforming unconditioned stimuli into signals of conditioned reflexes, clearly demonstrated in the foregoing experiment, is very important in regulating a number of physiological processes. This largely determines the combination of various unconditioned reflexes into complex reflex acts, in which one reflex process becomes a conditioned stimulus for another reflex process.

Suspension of action of various agents as conditioned stimulus. Discontinuance of the stimulation of receptors may also serve as a stimulus evoking a conditioned reflex. Owing to the activity of the cerebral cortex discontinuance of any stimulation of the receptors, just as different intervals elapsing after it, may become signals provoking any activity of the organism.

For example, if a noxious stimulus is applied every time at the moment when, say, a trumpet ceases to sound, then the end of this sounding becomes a stimulus which, due to the elaborated temporary connection, produces a defensive conditioned reflex. The dog remains absolutely quiet as long as the trumpet plays, but as soon as the sound of the trumpet ceases, the dog becomes restless: it jerks away the paw subjected to electrocutaneous stimulation, whines, etc.

Conditioned reflexes to time. The cerebral cortex is able to react to different intervals between its stimulations. For example, if food is always given to the dog at definite intervals, say, every ten minutes, then by the end of the tenth minute after the beginning of the previous feeding the animal will begin to secrete saliva and to exhibit a motor alimentary reaction. The "time measuring" by the cerebral cortex is probably based on traces of stimulations and on impulses coming to it from the receptors of the organs that function rhythmically (the heart and the respiratory system); when the intervals are longer this phenomenon is, probably, connected with the stimulation of receptors which depends on the state of the digestive organs, duration of the periods of wakefulness, etc.

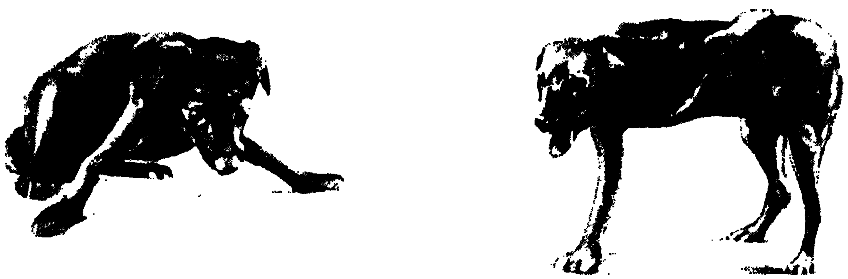

Fig. 271. Reproduction of cataleptic state in dog by agents previously combined with hypodermic injection of bulbocapnine (after A. Dolin).

Formation of conditioned reflexes to processes evoked by chemical stimulation of central nervous system. Possessing particularly high reactivity the cells of the cerebral cortex react both to changes in the composition of the blood by which they are bathed and to stimulation of the chemoreceptors. Changes in the state of the cerebral cortex resulting from introduction of various substances into the blood, can be used as unconditioned stimuli for elaboration of conditioned reflexes. In this case the agent, which has become a conditioned signal of the reaction resulting from the modification of the blood composition, evokes this reaction without (or prior to) the introduction of a corresponding chemical agent into the organism.

If the action of a stimulus which by itself never provokes vomiting (for example, phonation of a certain tone) repeatedly coincides in time with the introduction into the blood of a substance stimulating the cells of the vomiting centre (apomorphine, or morphine in dogs), a typical conditioned reflex is soon elaborated: the previously indifferent agent (tone) reproduces the full picture of vomiting (N. Podkopayev, V. Krylov).

Conditioned reflex reproduction of pathological changes. The action of an indifferent agent can be combined with a simultaneous emergence of pathological processes; in this case the latter, owing to the elaboration of temporary connections, will arise under the action of this indifferent agent alone.

For example, the subcutaneous injection of a certain toxic agent—bulbocapnine—leads to the emergence of *catalepsy*, which is characterized by an exceptional increase in the so-called plastic tone, due to inhibition of the motor zone of the cerebral cortex (p. 657); the skeletal muscles become set for a long time in the shortened or stretched state which has been imparted to them. If some agent, for example, the sound of gurgling liquid, is combined with the simultaneous action of bulbocapnine, after 10 to 12 combinations of this sound with the injection of bulbocapnine, the gurgle alone (in the presence of all conditions in which the injection of the poison is usually performed) evokes catalepsy (A. Dolin); in this state of conditioned reflex catalepsy it is possible to place the dog in most extraordinary postures (Fig. 271).

This group of phenomena also includes a sharp rise in blood pressure under the action of an agent which was connected with the injection of adrenalin (A. Makarychev), and changes in the work of the heart under the action of agents signalling the injection of cardiac poisons (p. 125).

In their practical work physicians must always consider the possibility of elaborating conditioned reflexes to agents coinciding in time with pathological processes; similarly, "neutral" agents coinciding in time with an improvement in the patient's condition due to elaboration of conditioned reflexes, may produce valuable therapeutic effects.

Conditioned Reflexes of Superior (Second and Subsequent) Order

Conditioned reflexes can also be elaborated through reinforcement of any previously indifferent stimulation by an agent which evokes not an unconditioned but a previously elaborated conditioned reflex.

For example, light accompanied by some sound, which was transformed by alimentary reinforcement into an alimentary conditioned stimulus, will after a number of combinations with this sound evoke the same conditioned reflex as the sound itself (in such experiments combination of an indifferent and conditioned stimuli is, of course, not accompanied by any unconditioned stimulus). This is the case when conditioned reflexes of the second order are formed.

D. Fursikov elaborated in dogs conditioned reflexes of even the third order. Mechanical stimulation of the skin on the paw was a conditioned stimulus of the first order and was reinforced by electrocutaneous stimulation of the paw. A conditioned reflex of the second order was elaborated to the gurgle of liquid, combined with stimulation of the skin, while phonation of a tone combined with the sound of gurgling liquid (of course, without any reinforcement by cutaneous stimulation) was transformed into an agent evoking a conditioned reflex of the third order.

Conditioned reflexes of the second order were also elaborated to a conditioned reflex caused by stimulation of the interoceptors.

Conditioned reflexes of the second order can be elaborated only subject to a definite correlation between the time of action of the conditioned stimuli of the first order and those of the second order. To evoke a conditioned reflex of the second order in the dog by means of an indifferent agent the action of this agent must be suspended at least 10 seconds before application of the stimulus which produces a conditioned reflex of the first order. If this is not observed and the conditioned stimulus of the second order continues to act simultaneously with the conditioned stimulus of the first order (or ceases to act less than 10 seconds before it), no conditioned reflex of the second order can be elaborated; moreover, even the response to the conditioned stimulus of the first order disappears.

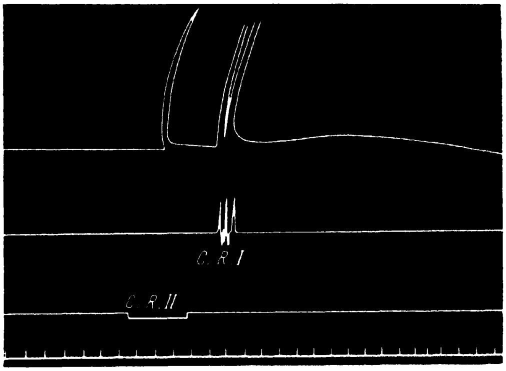

Fig. 272. Conditioned defensive reflex of second order elaborated through reinforcement of sound of buzzer by interoceptive conditioned stimulus (stimulation of mechanoreceptors of small intestine), which develops defensive conditioned reflex of first order.

Top to bottom: record of movements of paw; mark of rhythmic stimulation of duodenum (*C.R. I*); mark of action of conditioned stimulus of second order (*C.R. II*); time interval (one second) (after E. Airapetyants).

This is accounted for by the fact that the combination of two stimuli in all these experiments, is, of course, not reinforced by any unconditioned reflex or the complex stimulus would merely produce a conditioned reflex. But nonreinforcement creates conditions for the development of inhibition in the cerebral cortex. If some agent acts simultaneously with the conditioned stimulus (or ceases less than 10 seconds before it begins to act) and this combination is not reinforced by an unconditioned reflex, then a conditioned inhibitory agent is elaborated (p. 631). But if ten (or more) seconds elapse between the suspension of the action of agent *A* and the beginning of the action of the stimulus which evokes a conditioned reflex of the first order, agent *A* becomes a stimulus producing a conditioned reflex of the second order. The mechanism of these delicate relations is not yet sufficiently clear.

Elaboration of Temporary Connections Between Foci of Cortex Stimulated by Indifferent Agents

Temporary connections are formed not only when the action of some previously indifferent stimulus coincides in time with that of the agent which produces an unconditioned (or already elaborated conditioned) reflex; a temporary connection between two (or more) groups of neurons of the cerebral cortex is also formed when stimulation of the receptors provokes neither an unconditioned (except, orienting) nor a previously elaborated conditioned reflex.

If, for example, light and the sound of a bell, which were never reinforced by an unconditioned stimulus and did not evoke any responsive activity, except orienting reactions, are applied dozens of times simultaneously, excitation of these cells becomes, as it were, united. If one of the two simultaneously applied indifferent agents—the bell—is subsequently transformed into an alimentary conditioned stimulus through its reinforcement by the act of eating, and if after that the light stimulus is applied separately, it produces, as does the bell, a similar alimentary conditioned reflex, although it was never accompanied by feeding.

These experiments carried out in Pavlov's laboratory were later repeated and corroborated. For example, stimulation of the intestinal interoceptors was combined with stimulation of the receptors of the muscles which occurred during the flexion and extension of the paw. The flexion and extension of the paw were later transformed into an alimentary conditioned stimulus. Owing to this, the stimulation of the intestinal receptors, which had itself never been combined with feeding, also turned into an alimentary conditioned stimulus, under the action of which the dog salivated, licked its lips, reached for the place from where the food receptacle was presented and at the same time lifted its paw (Airapetyants).

N. Krasnogorsky showed that temporary connections between several cortical structures stimulated from various receptors were easily elaborated in children. Combining the simultaneous action of several indifferent agents, it is possible to form in children long chains of stimuli linked by a temporary connection. When a conditioned reflex is elaborated to *one* agent of this chain through its reinforcement by an unconditioned stimulus, all the previously indifferent stimuli, which mutually reinforced each other, are also included in the temporary connection with the unconditioned reflex.

CHAPTER 61

INHIBITORY PROCESSES IN CEREBRAL CORTEX*

The normal activity of the cerebral cortex necessarily involves unceasing interaction between processes of *excitation* and *inhibition:* the former leads to the elaboration and effectuation of conditioned reflexes, the latter to their suppression.

Two forms of cortical inhibition are distinguished depending on the conditions under which inhibition emerges: unconditioned, or inborn inhibition (external and transmarginal) and conditioned, or elaborated (the latter is often designated as internal).

Unconditioned Inhibition of Conditioned Reflexes

External inhibition. External inhibition of conditioned reflexes arises when the organism is acted upon by a conditioned stimulus and is simultaneously stimulated by an agent which evokes a different reflex. In other words, external inhibition of conditioned reflexes is due to the fact that during the excitation of the cortical centre of a conditioned reflex another focus of excitation arises in the cerebral cortex. For example, natural alimentary conditioned reflexes are inhibited if, while the dog is shown meat, an electric bulb of 500 candle-power is switched on before its nose, or its tail is pinched, or a cat appears before it, etc. Very stable and strong conditioned reflexes are inhibited with greater difficulty than weaker reflexes.

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* Parts of this chapter, in particular, the description of the phenomena of hypnosis written by the late Professor N. Podkopayev, are given according to the first and second editions of the text-book.

If an extraneous stimulus, whose application caused external inhibition of the conditioned reflexes, evokes only an orienting reflex (for example, the sound of a bell) its repetition leads to the disappearance both of the orienting reflex and of its inhibitory action (*extinctive inhibitor*).

But if an agent acting during the accomplishment of a conditioned reflex evokes not an orienting, but a different unconditioned reflex, which is not weakened with frequent repetition, its inhibitory action does not diminish. For example, alimentary conditioned reflexes are inhibited every time the centre of urination is excited during the action of stimuli which evoke them.

The outcome of the conflict of excitatory processes, evoked by different stimuli in the cerebral cortex, is determined by their strength and functional role. Weak excitation irradiating over the cerebral cortex often intensifies rather than inhibits the conditioned reflexes (phenomena of facilitation and dominant), while strong excitation inhibits them.

Under simultaneous action of two conditioned stimuli, which are signals of different unconditioned stimuli, these conditioned reflexes may inhibit each other due to the mechanism of external inhibition.

As regards the mechanism of its emergence, external inhibition of conditioned reflexes is similar to that observed in other parts of the central nervous system; its emergence does not require any definite conditions of action of the inhibitory stimulus. Pavlov, therefore, designated it as unconditioned inhibition.

Transmarginal inhibition. If the intensity of the conditioned stimulus exceeds a certain limit, the result is not intensification, but weakening or total inhibition of the reflex. Similarly, simultaneous application of two strong conditioned stimuli, each of which, taken separately, evokes a pronounced conditioned reflex, weakens the conditioned reflex.

The cortical cells are also inhibited when the action of the stimulus on the same cortical structures is frequently repeated, i.e., when the same conditioned stimulus is applied repeatedly, at short intervals. Any frequently repeated conditioned stimulus unalternated with other conditioned stimuli becomes inhibitory.

Inhibition developing in the cortical cells in response to strong, frequent, or long-continued stimulation was characterized by Pavlov as *transmarginal inhibition* since it arises when excitation exceeds the limit of efficiency of the cortical cells in the given animal and in its given state. In other words, the nerve cells have a certain *strength limit* of excitation beyond which any further intensification (or prolongation) of the excitatory process replaces excitation by inhibition.

Transmarginal inhibition may also manifest itself in the form of pathological exhaustibility of the excitatory process. In this case the excitatory process, which begins normally, is very soon interrupted, and succeeded by inhibition.

Internal (Conditioned) Inhibition and Its Forms

Internal, or *conditioned* inhibition, characteristic of the activity of the higher division of the nervous system, arises when the conditioned stimulus is not reinforced by an unconditioned reflex. Internal inhibition, consequently, emerges in the absence of the principal condition for the formation of a temporary connection, namely, coincidence in time of the two foci of excitation created in the cortex by the action of the conditioned stimulus and its reinforcing unconditioned stimulus.

If the conditioned stimulus is repeatedly applied without any reinforcement, it evokes a process of inhibition in the same structures of the cerebral cortex in which previously it produced excitation. Thus, alongside positive conditioned reflexes there are ***negative, inhibitory*** conditioned reflexes. They manifest themselves in the suppression, suspension, or prevention of excitation in the organs of the body, whose activity was provoked by the given positive conditioned stimulus before it had been transformed into an inhibitory stimulus.

The following four groups of cases are distinguished in internal inhibition, depending on the conditions under which the conditioned stimulus is not reinforced by an unconditioned stimulus: ***extinction, differentiation, retardation*** and ***conditioned inhibition.***

Extinction. If the conditioned stimulus is applied several times in succession without reinforcement by an unconditioned stimulus, the conditioned reflex gradually diminishes and, in the end, disappears. The shorter the intervals between the applications of the nonreinforced conditioned stimulus, the quicker the development of inhibition, i.e., the sooner the effect of the conditioned stimulus is extinguished and reduced to zero. If after its full extinction an interval is made in the application of the nonreinforced conditioned stimulus, the conditioned reflex evoked by it will after some time recover. Consequently, being extinguished, the conditioned reflex does not disappear, but is retarded, while the temporary connection is switched off by the process of internal inhibition.

Differentiation. Differentiation is a form of internal inhibition; it arises under the action of agents not reinforced by any unconditioned stimulus and similar to the agent which is regularly reinforced and which among other similar stimuli becomes the only one able to produce a positive conditioned reflex.

This somewhat complicated definition can be easily explained by an example. If a defensive conditioned reflex has been elaborated, say, to weak mechanical stimulation of the skin on the thigh reinforced by the application of an electric current, then owing to primary generalization of the conditioned reflex (p. 617) mechanical stimulation of any area of the skin will also produce a defensive conditioned reflex. But if the stimulation of the skin of the trunk, neck, or leg is never reinforced by an electric current, while only stimulation of the skin on the thigh is reinforced by it, a *differentiation* is elaborated: stimulation of the skin on the thigh will always evoke a defensive conditioned reflex, whereas stimulation of all other areas of the skin will not, due to emergence of internal inhibition.

Not only similar stimulations of exteroceptors, but also similar stimulations of the interoceptors are differentiated from each other. A defensive reflex to the introduction of a weak solution of acid into the intestine can be differentiated from the stimulation caused by the introduction of water into the intestine.

Elaboration of differentiation is very important for the normal activity of the organism, since in the course of its normal existence similar agents constantly act upon it, and only one among them actually represents a signal of a certain unconditioned stimulus. Owing to the elaboration of differentiation, the phenomena of the external and internal environment are broken up into agents which exert different physiological influences;

only the agents which precede the action of an unconditioned reflex evoke the given conditioned reflex. All other agents become inhibited.

Elaboration of differentiations is a perfectly objective method of ascertaining the discriminative abilities of the analysers. It has been found that dogs are able to differentiate between a metronome rhythm of 100 beats per minute, reinforced by feeding, and a rhythm of 96 beats per minute not reinforced by feeding. It has also been established that dogs very well discriminate between various forms of figures and degrees of illumination of objects (shades of gray and white), while most dogs are unable to differentiate between colours.

Two similar stimuli are often accompanied by different unconditioned stimulations; for example, a high tone, by feeding; a low tone, by application of an electric current to the skin. In these cases differentiation between two stimuli also occurs owing to the processes of cortical induction (p. 640).

Conditioned inhibitory agent. If a positive conditioned stimulus is applied in combination with another agent and is not reinforced by an unconditioned stimulus, the conditioned reflex to the combination of stimuli disappears owing to the development of internal inhibition. The agent, in combination with which the conditioned stimulus is not reinforced by an unconditioned stimulus, becomes a signal of nonreinforcement and a *conditioned inhibitory agent.*

Let us suppose, by way of example, that the sound of a metronome with a frequency of 120 beats per minute is continuously reinforced by unconditioned stimulation, while the sound of a metronome acting simultaneously with a flashing light is not reinforced by any unconditioned stimulus. The combined stimulus, i.e., the metronome plus the light, will inhibit the conditioned reflex. The light will become a conditioned inhibitory agent—a signal of nonreinforcement—and will also inhibit other conditioned reflexes.*

Conditioned inhibition is elaborated only when the agent, in whose presence the conditioned stimulus is not reinforced, acts either simultaneously with the conditioned stimulus, or a few seconds before it. If the action of this agent ceases 10 and more seconds before the conditioned stimulus, a conditioned reflex of the second order is elaborated.

Retardation. The processes of internal inhibition also play an important role when there is a more or less long interval between the beginning of the action of a conditioned stimulus and that of an unconditioned stimulus. In this case the conditioned stimulus is not reinforced during a certain period of time which elapses from the beginning of its action and is, therefore, subject to inhibition. For example, if the time of isolated action of the conditioned stimulus is prolonged to 2 or 3 minutes and more, a process of internal inhibition arises in the first phase of action of such a stimulus and a process of excitation in the second phase. As a result, the effect produced by this conditioned stimulus manifests itself only by the end of its action, closer to the moment when the unconditioned stimulus begins to act. These are cases of retarded conditioned reflexes (Table 28).

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* An agent, in whose presence the conditioned stimulus is not reinforced and which, being a signal of nonreinforcement, evokes inhibition in the cortex was termed by Pavlov a conditioned inhibitory agent (in 1907). In 1935 Pavlov stated that all cases, which were designated as internal inhibition, should be termed as conditioned inhibition. At that time Pavlov considered conditioned inhibition to be essentially a more complex form of differentiation.

Table 28

Record of Experiment with Retarded Alimentary Conditioned Reflex (after Pavlov)

Time	Conditioned stimulus applied for three minutes	Salivary secretion every 30 seconds in drops
3 hours 12 minutes	whistle	0-0-2-2-4-4
3 " 25 "	"	0-0-4-3-6-6
3 " 40 "	"	0-0-2-2-3-6

The interval constantly observed between the beginning of the action of the conditioned stimulus and the beginning of the accomplishment of the conditioned reflex—the so-called latent period—depends mainly on the development of internal inhibition and is none other than the period of retardation of the conditioned reflex.

During the accomplishment of conditioned reflexes the duration of the interval between the stimulation of the receptors and the beginning of the reaction of the effectors is determined mainly by the development of retardation, i.e., inhibition (Bykov and Petrova). In a number of cases conditioned reflexes are effected even quicker than unconditioned reflexes. For example, under the action of cold (or heat), uninfluenced by natural conditioned stimuli, which are usually connected with cooling or heating, the processes of thermoregulation appear only after about half an hour of such cooling or heating. But in the presence of conditioned stimuli the process of thermoregulation appears within several minutes.

Inhibitory conditioned reflexes. The process of internal inhibition, arising under the influence of any of the aforesaid conditions, may become connected, just as in the formation of positive conditioned reflexes, with a certain indifferent agent. If a conditioned reflex is extinguished, i.e., reduced to zero, and then a certain indifferent agent of medium strength is applied in combination with the extinguished, i.e., inhibitory, stimulus, after several combinations the isolated application of this indifferent agent will evoke an inhibitory process in the cerebral cortex (Y. Volborth).

Successive inhibition. Inhibition dissipates only gradually; phenomena of inhibition, arising in the cerebral cortex under the action of inhibitory agents, persist for some time even after discontinuance of the stimulation by which they were evoked. Therefore, if several minutes after stimulation evoking conditioned inhibition a positive stimulus is applied, its action will prove to be weakened. This is particularly pronounced if the applied positive stimulus is directed to the same cortical analyser, which was influenced by the inhibitory agent.

Phenomena of disinhibition. If an extraneous stimulus is applied to the experimental animal (for example, if a strong bell is used during the development of extinction or the action of a differentiation) during the action of an agent, which evokes in the cerebral cortex internal (conditioned) inhibition the process of inhibition disappears. It is, as it were, washed off by excitation which irradiates from the cortical cells receiving the action of the extraneous stimulus (an agent not included in the system of conditioned reflexes of the given animal). This disappearance of inhibition under the action of excitation which, so to speak, washes it off, is called *disinhibition*. It arises under the influence of stimuli which evoke external inhibition of positive conditioned reflexes.

Disinhibition is also observed if a certain extraneous stimulus is applied during the phase of the inhibitory action of retarded reflexes; the conditioned reflex also manifests itself during this phase.

Active Nature of Cortical Inhibition

The development of internal inhibition leads to the disappearance of the effect (for example, of the salivary conditioned reflex) produced by the conditioned stimulus. Similarly no conditioned reflex is observed when the cortical cells are in a state of rest, i.e., when not stimulated by any agent.

It is easy to see, however, that the state of inhibition of the cerebral cells differs from the resting state. In addition to the phenomenon of disinhibition, which could not occur if inhibition were identical with rest, this is indicated by other facts. Inhibition in the cerebral cortex is a reaction of the cortical cells to stimulation, which sharply differs from the state of rest that results from the absence of any stimulating agents. Furthermore, inhibition is characterized by the fact that it may vary in intensity and can *irradiate over the cerebral cortex*; it spreads from the cortical cells where it arises under the influence of the stimulation which inhibits these cells. All this testifies to the fact that inhibition of the cortical cells is not absence of activity, but a specific form of activity; that it is not a state of rest, but an active process. Its intrinsic nature is still unknown, but at any rate, internal inhibition is, as Pavlov indicated, not identical with fatigue.

The inhibitory process is intensified by repeated action of the inhibitory stimulus. If, for example, a certain conditioned reflex has already been totally extinguished, i.e., if the response of the effectors to the action of the nonreinforced conditioned stimulus is no longer in evidence, it is possible to intensify the inhibition by further application of the inhibitory stimulus. This manifests itself in the duration and strength of successive inhibition.

Let us suppose, by way of example, that as a result of the extinction of an alimentary conditioned reflex to a metronome by its application every three minutes without food reinforcement, this agent already after the eighth nonreinforcement ceases to evoke a salivary conditioned reflex. After that no stimuli are applied for 30 minutes. Following this interval the conditioned reflex to the metronome recovers, say, 50 per cent; this means that 30 minutes after total extinction the action of the metronome again produces half the amount of saliva which characterizes the normal conditioned salivary reflex to this agent. In another experiment, after the metronome again exhibits zero effect following the eighth nonreinforcement it is used four more times without reinforcement (with the same 3-minute intervals between the tests). Now, as in the first experiment, after an interval of 30 minutes, the metronome evokes no secretion of saliva. It follows that after the conditioned reflex has already been fully inhibited further application of the metronome without reinforcement leads to intensification of inhibition expressed in its prolonged aftereffect.

By using delicate differentiations, i.e., differentiations in which the nonreinforced stimulus differs very little from the reinforced stimulus, for example, when elaborating a differentiation to a sound differing from the reinforced sound only by one-eighth of a tone, we observe greater inhibition than when a coarse differentiation is used—for example, to a sound differing from the reinforced sound by a half-tone. Successive inhibition resulting from a delicate differentiation is more protracted.

Thus, the process of inhibition in the cerebral cortex is characterized by different intensity which in some measure depends on the physical strength of the inhibitory stimulus.

Development of inhibition is often difficult for the nervous system. Impeded development of inhibition is observed, for example, when the inhibitory and excitatory processes develop in closely situated points of the cortex (say, when a differentiation is elaborated to stimulations of adjacent areas of the skin, or to close tones) or when the inhibitory stimulus acts immediately after the positive stimulus.

Pavlov emphasized that the nervous system coped with the solution of difficult tasks best when there was a *gradual* transition from easily elaborated forms of inhibition to more difficult forms. For example, an attempt to produce an immediate differentiation between the frequency of a positive stimulus—metronome with 100 beats per minute (always reinforced by feeding) and a very close metronomic rhythm of 96 beats per minute (not reinforced by feeding)—will result in some "breakdown" of the higher nervous activity: inhibition of the positive reflex, or, on the contrary, general excitation, disinhibition of the previously elaborated differentiations and hypnotic phases. But if the differentiation is elaborated gradually—for example, first between 60 and 100 beats of the metronome per minute and then 80, 90 and 94 beats per minute—a very delicate differentiation can finally be obtained.

Generally speaking, the process of inhibition is always connected with the process of excitation. Pavlov repeatedly stressed the complexity of this process. He wrote: "... the question of the relation between excitation and inhibition still baffles solution. Is it the same process interchanging under definite conditions, or two processes, strongly knit together, revolving under certain conditions and showing now more or less and now fully both their aspects?"*

Inhibition and excitation are different aspects of a single process; inhibition can arise only under the influence of stimuli which evoke it and which usually act upon the cerebral cortex from the receptors.

The process of cortical inhibition is more susceptible to various influences than the process of cortical excitation. Pavlov found that experimental lesions of the cerebral cortex, for example, extirpation of separate cortical sections, affected the processes of conditioned (internal) inhibition most: after such destruction of a part of the cerebral cortex positive conditioned reflexes recover quite rapidly, the coarsest differentiations are re-established much later, while the delicate differentiations are irretrievably lost. Similar derangement of cortical inhibition is often observed in experimental neuroses and in intoxications (A. Ivanov-Smolensky). In these cases inhibition either greatly weakens, which leads to an abnormally extensive irradiation of the process of excitation or, on the contrary, spreads to a considerable number of cortical structures.

Irradiation of Inhibitory Process Over Cerebral Cortex

The process of inhibition, like that of excitation, arising in the cerebral cortex does not remain at the site of its origin, but spreads over the cerebral cortex. This phenomenon is called *irradiation of inhibition.* It is much more pronounced in the cerebral cortex than in the lower divisions of the central nervous system.

Irradiation of excitation over the cerebral cortex has already been described earlier as a process which underlies formation of temporary connections and the phase of generalization of conditioned reflexes.

The phenomenon of irradiation of inhibition over the cerebral cortex was discovered in Pavlov's laboratory in a number of experiments (N. Krasnogorsky, D. Fursikov, B. Kogan et al.).

For example, three little apparatuses for rhythmic mechanical stimulation of the skin—so-called "touchers"—were fastened to the skin of the thigh and leg of the animal. Stimulation of a certain lower point on the leg by an "inhibitory toucher" was differentiated through constant nonreinforcement by an alimentary unconditioned stimulus from the stimulation of two other points, and therefore did not produce a single drop of saliva. Stimulation of the two other points of the extremity by the "positive touchers" was always accompanied by food reinforcement and produced an alimentary conditioned reflex of a constant value. Stimulation 15 seconds after application of the inhibitory "toucher," equally inhibited the alimentary conditioned reflex in response to the stimulation by both positive "touchers." Ninety seconds after application of the inhibitory "toucher" stimulation by a positive "toucher," applied 15 cm. away from the site of the inhibitory stimulation, produced a normal effect, whereas stimulation by a positive "toucher" applied near the inhibitory "toucher" (5 cm. away) produced a considerably weaker conditioned reflex than usual.

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* I. Pavlov, *Complete Works*, Vol. III, Book 2, pp. 207-08.

This is accounted for by the fact that a process of inhibition arose in the cells of the cutaneous analyser of the cerebral cortex, stimulated by the inhibitory "toucher," and irradiated over the cortex (in the given case) embracing all cells of the cutaneous analyser in 15 seconds. The conditioned stimulation by the positive "touchers" applied at that time reached the inhibited cells of the cortex, owing to which the conditioned reflex sharply diminished; 90 seconds after inhibitory stimulation the cortical cells, situated farther from the site where inhibition originated, were already free from inhibition, and the latter gathered anew, as it were, around the point of its origin, but unable as yet to leave the cortical cells situated closer to those stimulated by the inhibitory "toucher." That is why 90 seconds after inhibitory stimulation the positive "toucher," farthest from the inhibitory "toucher," already produced the usual response, while the closer "toucher" still evoked a weakened reaction.

The rate at which inhibition is irradiated and subsequently concentrated depends on the type of nervous system and intensity of inhibition.

Transitional Phases Between Excitation and Inhibition

During the transition of the cortical cells from the state of normal excitability to total inhibition, i.e., at different degrees of their inhibition, the reaction of these cells to stimulation passes through a number of phases (which was first demonstrated in Pavlov's laboratory by I. Razenkov). These phases are characterized by different relations between the intensity of the reflex and the strength of the conditioned stimulus. Normally the effect of excitation in the nerve cells is the greater, the stronger (to a certain limit) their stimulation (Fig. 273, *A*). When the cells of the cerebral cortex begin to pass into a state of inhibition, the effects to all stimuli are the first to be equalized (usually because of a decrease in the excitatory effect to strong stimuli). This is the so-called *equalization phase* (Fig. 273, *B*).

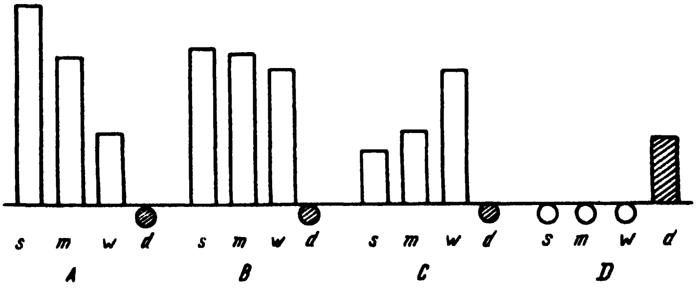

Fig. 273. Diagram illustrating transitional hypnotic phases.
S—strong stimulus; *m*—stimulus of medium strength; *w*—weak stimulus; *d*—differentiation (inhibitory) stimulus. *A*—normal force relations; *B*—equalization phase; *C*—paradoxical phase; *D*—ultraparadoxical phase. Heights of columns indicate values of conditioned reflexes.

If the inhibitory process is further intensified, the conditioned reflexes to strong stimuli almost disappear, while to stimuli of medium strength they weaken, and to weak stimuli do not change at all. This is the *para-*

doxical phase in which the relations between the intensity of the conditioned reflex and the strength of the conditioned stimulus are greatly distorted (Fig. 273, *C*).

A so-called *narcotic* phase is sometimes observed during transition of the cortical cells to inhibition. In this phase all conditioned reflexes weaken, so that they may totally disappear to weak stimuli and markedly diminish to strong stimuli. The place of this phase among the others is not clear as yet.

When the inhibitory process is still more intensified, the conditioned reflexes to all positive stimuli completely disappear, while the action of inhibitory conditioned stimuli shows a positive effect. This phase is called *ultra-paradoxical* (Fig. 273, *D*), and is a reaction so far observed only in the cerebral cortex. Finally, during transition of the cortical cells to a state of complete inhibition all effects to all conditioned stimuli disappear.

Normal Sleep as Process of Inhibition Irradiated Over Cerebral Cortex; Phenomena of Hypnosis

When conditions for extensive and protracted irradiation of inhibition over the cerebral cortex are created, the latter is no longer excited by stimulations from the external environment, and no longer acts on the skeletal muscles: the head drops, the eyelids close and the body becomes limp. The animal lies with its eyes closed and muscles relaxed and does not respond to acoustic, optic or other stimulations; in other words, it falls asleep.

Numerous experiments performed by Pavlov's school (N. Rozhansky, B. Bierman et al.) have shown that sleep arises when stimuli which have become inhibitory reach the cerebral cortex without opposition from positive conditioned stimuli. For example, if the same conditioned stimulus is applied often, the cortical cells receiving this stimulation pass into a state of inhibition and the latter irradiates over the entire cortex—the animal falls asleep. In dogs this state develops with particular ease when thermal or weak mechanical stimulations are applied to the skin.

Sleep also arises if the interval between the application of the conditioned and the unconditioned stimuli is prolonged: inhibition due to such retardation easily irradiates, and the animal falls asleep. The development of sleep under the action of inhibitory stimuli can be largely prevented if the inhibitory agents are opposed by stimuli which evoke diverse positive conditioned reflexes, i.e., if a mosaic of inhibitory and excitatory points is deliberately created in the cerebral cortex.

Thus, sleep is based on extensive irradiation of inhibition over the cortex which can also descend to the nearest subcortical structures.

Sleep may be evoked by any factor connected with the conditions under which it usually sets in in everyday life, for example, by lying in bed. The exclusion of positive conditioned and unconditioned stimuli acting upon the cerebral cortex is also important for the development of sleep (darkness, silence); likewise important is relaxation of the skeletal muscles which considerably reduces the flow of impulses from their receptors. The significance of the latter factor is confirmed by electrophysiological investigations which show that in a person falling asleep the tone of the skeletal muscles decreases, i.e., the muscular bio-electrical currents diminish or disappear.

The importance of the flow of impulses from the receptors to the cortex for the maintenance of the animal's alert, active state was first stressed by

Sechenov "with wonderful intellectual force," to use Pavlov's words. Pavlov elucidated the role of this flow of impulses exciting the cerebral cortex as a factor which counteracts the irradiation of inhibition over the cortex.

The following case convincingly proves the inevitable irradiation of inhibition over the cerebral cortex when stimulating impulses reach it (or when the impulses become inhibitory). Hysterical paralysis left a certain patient with only one functioning eye and one ear. As soon as the patient closed his functioning eye he immediately fell asleep. This phenomenon was experimentally reproduced by V. Galkin in the laboratory headed by A. Speransky: dogs with visual, auditory and olfactory receptors simultaneously removed by surgical operation slept from 20 to 23 hours a day. These dogs could be disinhibited only by strong stimulation of the cutaneous receptors. They were also awakened by hunger, i.e., by strong stimulation of the interoceptors.

The fact that animals deprived of the cerebral hemispheres also sleep and that sleep develops when definite areas of the floor and wall of the third ventricle are stimulated in no way contradicts Pavlov's concept of the physiological nature of sleep as a process of irradiation of inhibition originating in the cerebral cortex. Removal of the cerebral cortex still leaves conditions for irradiation of the inhibitory process over the subcortical formations. Emergence of a state of sleep due to stimulation of the lower divisions of the hypothalamic region could, according to Pavlov, affect the cerebral cortex like weak stimulations which very easily evoke sleep. At the same time this stimulation could block the conduction of impulses from the receptors to the cerebral cortex through the thalamus, i.e., act the way the closing of the eye did in the patient with his other receptors paralyzed, or the experimental exclusion of receptors in dogs by Speransky and Galkin, or the severe injury to the ascending reticular system in monkeys (Magoun).

During normal sleep the heart slows down, the blood pressure somewhat falls, metabolism decreases, the respiratory rate diminishes, the content of carbon dioxide and the concentration of hydrogen ions in the blood slightly rise, the kidneys excrete a larger amount of acid products and the temperature of the body slightly drops. These changes are undoubtedly connected with changes in excitation in the hypothalamic centres, but their actual cause is a more or less complete exclusion of the activity of the cerebral cortex, with the inhibitory process irradiating over it.

A change in all the functions of the organism during normal sleep usually occurs at night when it coincides with the change in the entire surroundings. But modifications of the "vegetative" functions are observed at night even when there is no night sleep. In persons who work night shifts, the pulse rate, blood pressure and content of carbon dioxide in the alveolar air show changes similar to those observed during sleep; it requires complete "distortion" of all conditions of surrounding life to replace sleep by wakefulness without any manifestations of the "somnolent" period of the day in the activity of the internal organs. For this reason during a trip in the latitudinal direction, for example, from Moscow to the Far East, where 10 a.m. corresponds to two a.m. in Moscow, all internal organs soon adapt themselves to the changes in the daily periodicity of life, while night-watchmen show no such adaptation.

Irradiation of inhibition over the cerebral cortex in no way completely excludes its functions. Though modified in the cerebral cortex during sleep, the action currents do not disappear (Fig. 283). Extensive inhibition of the mass of cortical cells, especially inhibition of various intensity, should not be regarded as complete exclusion of *all* the cortical functions from the activity of the organism. Inhibition of the cerebral cortex is a specific active state; Pavlov believed it impeded destruction and helped restore the substances utilized during the work of the brain.

By studying the nature of cortical electric potentials (electro-encephalograms) we obtain data coinciding with the foregoing facts ascertained by the method of conditioned reflexes. The action currents of the cerebral cortex sharply change during sleep. The rhythm of the electric waves slows down both during normal and hypnotic sleep.

The fundamental difference between sleep and hypnosis is that in the latter case the inhibitory process does not affect the entire cortex, but spreads to definite regions, as a result of which there are more or less considerable areas with normal excitability between the inhibited zones. When hypnotizing a person it is important to retain the activity of the second signalling system (Chapter 65), by means of which the physician establishes verbal contact with the patient for the purpose of treating him by suggestion.

The difference between hypnosis and natural sleep is only quantitative. In normal sleep the cerebral cortex (except, perhaps, for separate short periods of very profound sleep) is also incompletely inhibited. Against the background of diffused inhibition there always remain, so to speak, interspersed, isolated points which are either in a state of normal excitability or, more often, in one of the hypnotic phases. It is the activity of the cortical cells in the isolated, disconnected excited points which is the cause of dreams.

Protective Role of Inhibition

Transmarginal inhibition (p. 629) is a kind of protective mechanism. It guards the nerve cells against exhaustion, which would inevitably result if the intensity of excitation went beyond a certain limit, or persisted without interruption over a definite period of time.

A cortical cell, Pavlov wrote, "...being, so to speak, a sentry-post of the organism, is highly reactive and, therefore, very rapidly functionally destroyed and fatigued. The inhibition which arises, while not a phenomenon of fatigue in itself, appears in the role of a protector of the cell; it prevents further excessive and dangerous destruction of this exceptional cell. During the inhibitory period the cell, released from any activity, recovers its normal composition."* Transmarginal inhibition, protecting the cortical cells from exhaustion, may, therefore, also be called protective inhibition. This protective property is peculiar not only to transmarginal inhibition, but to sleep inhibition as well.

Not every manifestation of inhibition in the cerebral cortex can be regarded as transmarginal inhibition, otherwise each extinguished or differentiated stimulus, because of its nonreinforcement, would have to be considered as exceeding the strength limit (i.e., as transmarginal). Similarly, one can hardly regard as transmarginal inhibition the cases of unconditioned (external) cortical inhibition resulting from the action of weak unusual stimuli which evoke only a weak orienting reaction, but readily lead to the development of sleep. But this in no way means that the various cases of inhibition differ in nature and that transmarginal inhibition is a very special state. Pavlov was inclined to regard all cases of inhibition, in their essence, as manifestations of a single process inseparably connected with the process of excitation; he admitted that under certain conditions the energy of the excitatory process could be converted into the energy of the inhibitory process, and vice versa.

Transmarginal inhibition, initially arising in the cortical formations to which strong (or frequent, or protracted) stimulations are dispatched, can irradiate over the cerebral cortex and produce sleep.

Pavlov's theory of the protective role of inhibition has been substantiated by a number of experiments. It has been shown, for example, that after injection of various poisonous substances (tetraethyllead, bacterial toxins, mescaline) sleep, intentionally evoked by the administration of soporifics, contributes to a more rapid elimination of pathological disorders, which prior to this were sometimes even irreversible (A. Ivanov-Smolensky). Treatment by sleep produced appreciable results in the psychiatric clinic, especially in cases of schizophrenia and some other diseases. Beneficial effects of this method were also recorded—both experimentally and in the clinic—in the treatment of severe injuries to the skull and of shock (E. Asratyan). The so-called sleep therapy, i.e., the method of artificially prolonged sleep, has also yielded positive results in a number of other diseases.

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* *Ibid.*, Vol. IV. p. 263.

Is the protective significance of inhibition manifested in *all* cases of its development?

It would be difficult to give a final answer to this question; but since elaboration of inhibition is in a number of cases (for example, delicate differentiations) a very difficult task for the nervous system, it is doubtful that all manifestations of inhibition are protective. It is well known that in some cases of impeded development of inhibition concentrated inhibition is converted into irradiated inhibition, i.e., sleep. It is likewise known that as a result of certain pathological disturbances in cortical activity (for example, intoxication), concentrated inhibition is deranged and is often also succeeded by sleep.

It is possible that inhibition manifests its protective property with particular force only at definite degrees of intensity, especially when it easily irradiates. But the development of a more profound process of inhibition like excitation, probably, requires a certain amount of work on the part of the cortical cells and may provoke the operation of the protective mechanism resulting in a transition to less profound phases of inhibition, i.e., to easily irradiating inhibition. Although this conception is still hypothetic, it may help to interpret the difficulty with which the elaboration of delicate differentiations is connected, and the irradiation of inhibition frequently observed when the excitatory or the inhibitory processes are overstrained.

According to Bykov's assumption (made in 1952), the state of inhibition in the cerebral cortex and in the central nervous system in general is always connected with a change in the blood circulation, or, in a broader sense, in the "supply" of the inhibited nerve cells. The term "supply" signifies all the conditions under which the cells are supplied with and assimilate compounds, including oxygen consumed during their activity, and the elimination by the cells of the unused intermediate metabolites.

There are reasons to believe that all or many groups of nerve cells contain formations which function as receptors. It is possible that they are receptors in the true sense of the word; it is likewise possible that each cell has formations with receptive functions. This warrants the assumption that excitation of one group of cortical nerve cells can, by means of these receptive formations, i.e., reflexly, evoke changes in the blood circulation and in the supply of the other nervous formations functionally connected with them. Thus it can be assumed that in the course of cortical activity reflex changes may arise in the trophic functions of the cortical cells, in their supply with nutritive substances and in the conditions under which these substances are assimilated. At the same time the state of each group of nerve cells, probably, influences their own blood supply. Changes in the supply of oxygen and nutritive substances to the cortical cells (and changes in the elimination of metabolites) alter the functional state of these cells and their activity (it is a well-known fact that even a slight drop or rise in the tension of oxygen dissolved in the blood greatly influences the higher nervous activity). Modifications of the amount of blood flowing to some group of cortical cells, changes in the permeability of their superficial layer, in the permeability of the endothelium of the capillaries and in the properties of the glia must therefore substantially influence the activity of the cortical cells and the conditions of their transition to a state of inhibition or excitation.

Of course, it would be erroneous to reduce the question of intracortical transmission of nervous influences from one neuron to another to the conception of indirect interaction between them based on changes in the supply apparatus alone. But there is no doubt that all forms of cortical activity cannot be regarded one-sidedly, only as the result of impulsive-synaptic interactions between the neurons irrespective of all the conditions under which the cortical cells are nourished, conditions which change during the activity of these cells. Pavlov was far from treating this question so one-sidedly and constantly emphasized that the significance of nervous influences on the biochemical state of the tissues should not be overlooked.

CHAPTER 62

INTERRELATIONS BETWEEN EXCITATORY AND INHIBITORY PROCESSES IN CEREBRAL CORTEX. ANALYSING AND SYNTHESIZING ACTIVITY

Phenomena of Induction in Cortex

Induction signifies "the excitatory influence of one process upon another both in the circumference of the centre of the given process and the centre itself after the suspension of stimulation which directly provokes the process. This influence . . . is mutual, reciprocal: the process of excitation leads to intense inhibition, and the process of inhibition, contrariwise, leads to intense excitation. The former is designated by us as the negative phase of induction, and the latter as the positive phase of induction, or briefly—negative and positive induction."*

Positive induction consists in the fact that within a short period of time after application of an inhibitory stimulus, for example, of a differentiation, positive stimulation addressed to the same group of cells or to neighbouring cells produces a highly exaggerated conditioned reflex.

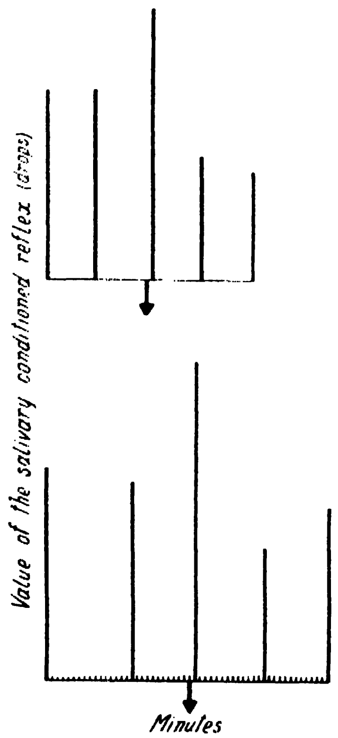

Fig. 274. Phenomena of positive induction.

Height of each line indicates value of conditioned salivary reflex: bottom, to mechanical stimulation of foreleg; top, to bright light. Inhibitory stimulus is indicated by arrow: bottom, to stimulation of hind leg; top, to weak light. Time indicated along the abscissa. (Taken from Pavlov's "Lectures on the Work of the Cerebral Hemispheres" and from experiments performed by D. Fursikov and L. Kalmykov.)

In each of the experiments demonstrated in Fig. 274 only one positive stimulus was applied, and one inhibitory stimulus to it—a differentiation—indicated by an arrow pointed downward from the abscissa. The figure shows that the positive stimulus applied immediately after suspension of the differentiation always yields a much bigger effect than normally. This is an example of manifestation of positive induction. With positive induction a state of heightened excitability arises in the cortical cells adjacent to those in which inhibition was evoked just prior to this. Because of the heightened excitability the impulses from the receptors, upon reaching the cortical cells when they are in a state of positive induction produce an exaggerated effect. Similar phenomena of induction also develop within the same group of cells after the action of inhibitory stimulus upon it.

Fig. 274 also shows that positive induction does not suppress the development of successive inhibition: during the long interval following application of the inhibitory stimulus (differentiation) the effect of positive stimulation, which was highly intense immediately after the inhibitory agent, diminishes.

Positive induction also manifests itself with great force in violent motor excitation, frequently observed in Pavlov's laboratory in dogs after their release from the experimental stands in which they were kept for hours without motion. In this case inhibition, evoked in the motor analyser by the long stay in the stand (with the collar fastened to the cross-beam, the legs strapped, etc.), was succeeded by strong excitation when the inhibitory stimulation was discontinued upon release from the stand.

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* *Ibid.*, p. 199.

Negative induction in the cerebral cortex consists in the emergence of inhibition in the cells surrounding the centre of excitation. It circumscribes the irradiation of excitation over the cerebral cortex.

Negative induction clearly manifests itself in experiments connected with removal of differentiations, i.e., when a differentiating stimulus (a "differentiation"), for example, a metronomic rhythm of 72 beats per minute, is transformed into a positive stimulus by food reinforcement. If the application of a differentiation is accompanied by feeding several times in succession, this differentiation is usually easily and quickly transformed into a positive agent. But if the differentiation reinforced by feeding alternates with the action of an invariably positive agent (for example, if a metronomic rhythm of 72 beats per minute alternates with another rhythm of 144 beats per minute, which is a positive alimentary stimulus), transformation of the differentiation is extremely impeded. The thing is that in the latter case (with definite intervals between the stimulations) the differentiation always gets into the phase of negative induction from a positive agent. This, despite the reinforcement of the differentiation, keeps up its inhibitory action.

Negative induction results in the emergence of inhibition around each group of excited cells in the cerebral cortex. When an external agent acts upon the organism, or when the interoceptors of the organism are stimulated, impulses from the receptors always reach the cerebral cortex where they create a focus of excitation. Inhibition is induced around it and this is manifested in the aforesaid external, or unconditioned, inhibition of the conditioned reflexes (p. 628).

As the differentiation is elaborated and consolidated irradiation of inhibition becomes less extensive and protracted.

The induction relations between the nervous processes prevent the irradiation of each of these processes over the cerebral cortex. Owing to them, the excited cells are surrounded by inhibited cells which are, consequently, in a state of lowered excitability; at the same time the focus of inhibition is surrounded by cells in a state of heightened excitability.

Positive induction arises at a certain medium intensity of the inhibitory process. At the same time the emergence of positive induction does not completely suppress successive inhibition: when a more or less considerable period of time elapses after the inhibitory stimulation, the stimulation of neighbouring points produces a weaker effect, even if, owing to induction, it earlier produced a strongly pronounced effect, since it was applied *immediately* after the inhibitory agent.

The study of the phenomena of induction is complicated because the processes of excitation and inhibition which determine them and their movement, continuously change in intensity and rate of irradiation over the cerebral cortex. It has been demonstrated, for example, that if the stimulation of a small area of the skin (about one cm. in diameter) performed with a "toucher" is only once not reinforced by food, stimulation of other areas of the skin for 10 to 15 minutes after this single nonreinforcement produces values of the conditioned reflex different from normal. The results of the experiments keep changing, as the experiments are repeated and inhibition is, so to speak, trained.

The movement of the cortical processes and the excitability of each cortical point fluctuate. Often positive induction is most pronounced at the point of the cerebral cortex closest to the centre of development of inhibition; at the same time inhibition distinctly manifests itself in the remoter sections of the analyser.

Generally speaking, phenomena of induction do not belong to the specific properties of the cerebral cortex like the phenomena of cortical coupling (elaboration of temporary connections) and conditioned (internal) inhibition. Phenomena of induction are clearly observed in the activity of the spinal cord; they have also been found by studies of the activity of receptors. There is a considerable external likeness between the phenomena of simultaneous and successive induction and the excitability changes at the poles of the action of a constant current observed in the nerve and muscle fibres (a catelectronus and an electronus, succeeded by excitation at the anodal region and inhibition at the cathodal region at the break of the current, p. 489). It is possible that such likeness to electrotonic changes in excitability depends on common physicochemical processes which underlie these phenomena.

Functional Mosaic of Cerebral Cortex

"... The infinite mass of natural phenomena," Pavlov wrote, "continuously produces positive and negative conditioned reflexes through the apparatus of the cerebral hemispheres and thereby determines the entire activity, the everyday behaviour of the animal in detail. Each of these reflexes must have its own point of application in the cerebral cortex i.e., its own cell or group of cells. One cortical unit is connected only with one definite activity of the organism, while another unit is connected with a different activity; whereas one unit evokes a certain activity, another prevents or suppresses it. Thus, the cerebral cortex is a grand mosaic, a grandiose signal board. Numerous reserve points always remain on this board for the formation of new signalling conditioned stimuli; in addition, the previously engaged points more or less frequently change their connections with various activities of the organism and their physiological significance."*

The functional mosaic in the cerebral cortex signifies the distribution (at every given moment and under definite conditions) of the excitatory and inhibitory processes over a mass of cortical cells, a distribution determined by stimulations acting at the given moment on the organism, by traces of previous stimulations (in the form of successive and irradiating inhibition and excitation, induction relations), and by temporary connections elaborated by the organism. The functional mosaic determines the activity of every animal at all times.

The elaboration of a delicate mosaic is sometimes a difficult task for the nervous system, but as the mosaic is elaborated it forms more and more easily.

In life there are frequent cases of delimitation between two excited cortical points, one of which is included in a temporary connection with one unconditioned (for example, alimentary) reflex and the other with another unconditioned (for example, defensive) reflex. This delimitation is due to negative induction arising around each excited cortical centre which has formed a temporary connection with cortical representations of different unconditioned reflexes, the latter in their turn being delimited by induction relations.

The stronger the unconditioned reflex (within certain limits), the wider the zone around the cortical cells excited at the signal of its action which becomes involved in a temporary connection with this reflex (owing to irradiation of excitation). But a weaker (and under the given biological conditions less essential) unconditioned reflex is connected only with a small zone of the cortical analyser situated close to the point directly receiving stimulation from the agent which signalizes it. For example, when one tone was the signal of a strong defensive reflex and another tone was the signal of an alimentary reflex, the entire nonreinforced scale of tones, except a very small section near the "food" tone, provoked this conditioned defensive reflex; the "food" tone, however, invariably produced only an alimentary conditioned reflex.

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* *Ibid.*, p 231.

Analysing and Synthesizing Activity of Cerebral Cortex

The activity of the cerebral hemispheres ensures constant analysis and synthesis of the stimulations both acting upon the organism from the external environment and arising in the organism itself. As externally opposite, as the phenomena of inhibition and excitation which underlie them, analysis and synthesis are inseparably bound up, and are unthinkable without each other.

Nervous synthesis means integration of the action of various stimuli upon the organism, their connection with certain functions through the reflex mechanism. All phenomena of coupling nervous connections between various agents stimulating the receptors and the responsive activity of the organism are manifestations of the synthesizing activity of the nervous system. Continuous coupling which ensures unconditioned, inborn reflexes is an elementary manifestation of the synthesizing activity; alternating coupling which ensures elaboration of temporary connections, owing to which the activity of the organism is determined by the conditions of action of each stimulus, by the *signalling significance of the stimulus,* is the higher form of synthesis—cortical synthesis.

A number of various agents of the external and internal environment always act simultaneously upon the organism by stimulating the huge mass of its diverse receptors. The equilibration of the organism with the varied conditions of existence is attained only by its different reactions to numerous changes in surrounding nature and the organism itself. The different reactions of the organism to various agents are possible only when each of these agents acts in its own peculiar way and is delimited in its action from all other agents.

Even little-differentiated lower animals and unicellular organisms react differently to various agents, if the latter are very dissimilar. Pavlov therefore pointed out that "lower degrees of analysis are, of course, also inherent in the lower divisions of the nervous system (as in the little-differentiated substance of animals without a nervous system), since even an organism deprived of the brain exhibits diverse reactions to stimulations of its external surface differing as regards the point of application, intensity and quality"* (and to different stimulations of its internal environment).

Pavlov regarded as *analysers* the totality of nervous formations which "isolate for the organism separate elements from the complexity of the environment...", each analyser "decomposing a corresponding part of the external environment into a long series of individual elements" and including a peripheral division—the receptors ("transformers, each of which converts only definite energy into a nervous process"), afferent nerves and their "cellular brain ends."**

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* *Ibid.*, p. 123.

** *Ibid.*, pp. 122-23.

The analysing activity is based on the process of inhibition, since this process alone checks the irradiation of excitation over the central nervous system. The stimulations singled out by the analysing activity are the more fractional, the more limited the irradiation over the centres of excitation which arises in them as a result of the stimulation of each receptor structure. The activity of the lower centres ensures only such form of analysis, as a result of which stimulation of each group of receptors evokes a different reflex response, which, however, is always relatively constant for the receptive field of each reflex. Such analysis is not only rough, but also static; the distribution of inhibition and excitation depends primarily on the kind of receptors from which the impulses come to the lower centres, and on their frequency and strength, but not on the conditions under which stimulations were previously applied to the organism.

The cerebral cortex ensures the effectuation of higher analysis based on conditioned inhibition which develops in the cortex, depending on the conditions of the action of the stimuli, on their reinforcement or non-reinforcement. Due to the process of internal, conditioned inhibition, from the mass of stimulations continuously reaching the cortex temporary connections with certain functions are formed only by the agents and complexes of agents whose action is reinforced by an unconditioned stimulus (or by a previously elaborated conditioned reflex).

The elaboration of differentiations is the most important factor in the analysing activity.

Schematically the differentiations can be divided into the following categories depending on the conditions of their elaboration: 1) differentiation of the *properties* of stimuli (height of tones, temperatures, forms of various objects, their colours and degrees of brightness, taste and olfactory agents, and agents acting upon the chemoreceptors of the blood vessels and tissues); 2) differentiation according to the *site* acted on by the stimulating agent (different areas of the skin, various skeletal muscles, tendons and ligaments) and according to the point of origin of acoustic, olfactory, visual, tactile and thermal stimulations; 3) differentiation of stimuli according to the *rhythm* of their application (different frequencies of auditory, cutaneous and optic stimulations, as well as stimulations of muscular receptors depending on the rhythm of muscular contractions); 4) differentiation according to the *strength* of stimulation; 5) differentiation according to the time and sequence of the application of stimuli.

Thus, impulses can be differentiated according to the quality, site, rhythm, strength and time of stimulation of the receptors.

Complex Conditioned Reflexes and Dynamic Pattern

Separate variations in the external and internal environment differentiated by the analysing activity of the cortex are associated by its synthesizing activity into diverse complexes of agents which, due to elaboration of temporary connections, are transformed into signals of various reflex acts.

Very often it is not a single stimulus which forms temporary connection with an unconditioned, or previously elaborated conditioned reflex, but a complex of stimuli acting on different groups of receptors or on different elements of one type of receptors, for example, on different areas of the retina, skin, intestinal tract, etc. It is possible to elaborate a complex conditioned reflex to combinations of simultaneously acting stimuli, for example, to the flash of an electric bulb and to a tone, to mechanical stimulation of the skin simultaneously with its cooling, etc. Complex reflexes can also be elaborated by a successive application of different agents. For example, if the following stimuli are successively applied for 20 seconds: light for 5 seconds, a tone for 10 seconds and mechanical cutaneous stimulation for 5 seconds, and the action of this successive series of stimuli is repeatedly reinforced by food (or by another unconditioned stimulus), a conditioned reflex arises to the complex of these consecutively acting agents.

If a complex conditioned stimulus has been elaborated from agents of different strength—a weak and a strong stimuli, each of which, taken separately, did not have any signalling property, the weak component of the complex, when applied alone, usually produces no conditioned reflex. Its action is overshadowed, as it were, by the strong component. The weak agent exerts certain action on the cortex just the same. This is proved as follows: if the weak component of the complex is transformed into an inhibitory stimulus by its separate application without reinforcement, the value of the conditioned reflex to the complex of the weak and strong agents markedly decreases.

After numerous reinforcements of the complex as a whole, its individual agents lose their effect if applied separately (in monkeys this occurs with greater ease than in dogs). Consequently, cortical synthesis is not a mere summation of the action of agents, but a formation of a new reflex act.

Differentiation of complex conditioned reflexes. If a certain complex of stimuli is constantly reinforced by food, and a complex of the same agents but acting in another sequence is not reinforced by an unconditioned stimulus, these complexes become differentiated. It has been shown (E. Asratyan et al.) that the same agent acquires different signalling properties depending on the conditions under which it acts. For example, by reinforcing the sound of a bell by alimentary stimulation in one room, and by electric stimulation of the skin in another room, it is possible to obtain an alimentary conditioned reflex with the help of the bell in the first room and a defensive conditioned reflex in the other.

The significance of the differentiation of complex stimuli becomes particularly obvious if we recall that one word is distinguished from another and one sentence is distinguished from another sentence only by a different sequence of sounds, syllables and words.

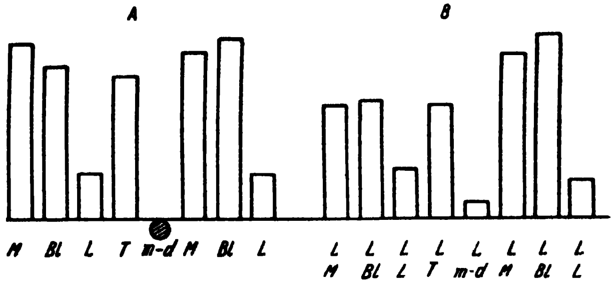

Fig. 275. Diagram of experiment with pattern *(A)* and with its replacement *(B)* by one stimulus (light).

Heights of columns indicate values of conditioned salivary reflex. *M*—metronome, Bl_1—bell, *L*—light, *T*—tone, *m-d*—differentiation to metronome.

Dynamic pattern. The synthesizing function of the cortex is also clearly demonstrated in experiments with conditioned reflexes elaborated according to the so-called pattern method. This method of elaborating conditioned reflexes consists in the fact that in the course of each experiment the conditioned stimuli are applied in an invariable order as regards their sequence and intervals between their application. The fixed order of phenomena of the external world is imprinted upon the activity of the cortex in the form of a "dynamic pattern," i.e., a single functional complex in which the action of an individual stimulus depends on more or less constantly recurring conditions and the sequence of this action in the series of other agents. This is proved, for example, by the following fact: if during one of the experiments the diverse stimuli of an elaborated pattern are replaced by the action of only one of them and the latter alone is applied at all points of the pattern, it will produce effects peculiar not to itself, but to the stimuli which occupied their respective points in the pattern (Fig. 275). These and other experimental data warrant the important conclusion that the cerebral cortex, which not only analyses, but also synthesizes all the stimulations received, functions as a very complex dynamic integral system.

Experiments show that the process of elaboration of a dynamic pattern entails certain difficulties for the cortex. At the same time the maintenance of an already established pattern is the easiest form of cortical activity. The reverse process—destruction of an elaborated pattern, and especially its replacement by a new one, likewise makes great demands on the cortical cells, which in certain cases may lead to pathological disturbances in higher nervous activity.

CHAPTER 63

TYPES OF NERVOUS SYSTEM AND FUNCTIONAL PATHOLOGY OF CORTICAL ACTIVITY*

Types of Nervous System

Practice shows that individuals of a definite species of animals possess, in addition to the general traits characteristic of all individuals of the given species, specific traits inherent in these individuals alone. This is also true of the functions of the cerebral hemispheres; it is precisely the various individual peculiarities in the activity of the cerebral hemispheres that are mainly responsible for the individual features of the organism's functions.

The activity of the cerebral cortex is characterized, in the first place, by a property which Pavlov called the *strength* of the nervous processes. The concept of strength ensues from the concept of the efficiency of the cortical cells; it relates both to the excitatory and inhibitory processes. It is well known that a strong stimulus produces a strong effect only when the intensity of the stimulus does not go beyond a certain limit. If this limit is passed, the excitatory process is succeeded by a process of inhibition, as a result of which the value of the reflex to such a supramaximal stimulus diminishes (transmarginal inhibition). Thus, it is possible to measure the *limit* of the working capacity of cortical nerve cells as regards the excitatory process they develop. Experience shows that there are *strong* types of nervous system, characterized by high efficiency, and *weak* types with low limit efficiency.

Furthermore, the activity of the cerebral hemispheres is characterized by the property of *equilibrium*. This term signifies the correlation or balance between the strength of the excitatory and inhibitory processes. Both processes may be of equal strength; in this case it is an *equilibrated* nervous system. But sometimes one process is more pronounced than the other, and then it is an *unequilibrated* type of nervous system.

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* This chapter was written by the late Prof. Podkopayev.

The third important property characterizing the work of the cerebral hemispheres is the *mobility* of the nervous processes. Since normally and under experimental conditions there are frequent cases when one process in a functional cortical centre must be rapidly succeeded by another process (for example, excitation by inhibition and vice versa), it is very important that the basic cortical processes be sufficiently mobile. Practice shows that there are *mobile* nervous types with one nervous process easily and rapidly followed by the other, opposite process, and inert, *stagnant* types in which this interchange is slow and difficult.

Classification of types of nervous system. Studies of a very large number of various experimental animals by means of special tests have revealed, at least as regards dogs, the following four principal types of nervous system:

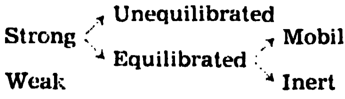
1. The *sanguine*, lively type. This is, so to speak, the ideal type in the centre of the classification. It has well-developed basic functional properties of the cortical cells: strong excitatory and inhibitory processes, both processes almost equally strong—equilibrated, and very mobile—both nervous processes rapidly and easily replace each other.

2. The *melancholic or weak type*. The most characteristic trait of the animals of this type is low efficiency of the cortical elements, which easily gives rise to transmarginal inhibition in them. In this type both the excitatory and inhibitory processes are weak, with the processes of inhibition predominating in the cortical dynamics. Dogs of this type show traits in their behaviour usually called timidity and cowardice. There are many variations within this type.

3. The *choleric*, or *impetuous* type. Both nervous processes are very strong in animals of this type but the excitatory process greatly predominates over the relatively weaker inhibitory process. Hence the characteristic trait of this type is disequilibrium. This type undoubtedly also has variations.

4. The *phlegmatic* or *calm* type. The characteristic trait of this type is lack of mobility, i.e., inertness of the cortical processes. Though the animals of this type sometimes have very strong and equilibrated nervous systems, their nervous processes replace each other slowly and with difficulty.

On the basis of the foregoing it is possible to draw the following diagram of the principal types of nervous system:



It will be observed that, like any classification, this is only a convenient scheme. In addition to the aforesaid types, there are various intermediate types.

The specific characteristics of each individual nervous system result from the complex interaction between the inborn traits and those acquired through the various interactions of the animal with the surrounding environment in the course of individual development. Experience shows that inherited traits may change essentially because of the high plasticity of the cerebral hemispheres. There are, for example, obviously cowardly dogs, but tests of their cortical activity show a strong and mobile rather than weak nervous system. There are also reverse cases. The cause of such divergence lies in the conditions under which the dogs were raised in the early period of their life. If a litter of newborn puppies is divided into two groups, of which one is constantly kept in a kennel and the other is raised under free conditions, the first group will show passive defensive reactions, while in the second group no passive defensive behaviour will be observed, though both groups include animals belonging to the same litter.

By careful training based on the knowledge of cortical activity it is possible considerably to "improve" the weak type of nervous system in dogs and to make it comparatively stronger. Thus, inherited traits are not something fatal and inevitable, but can be changed.

The concept of type of nervous system is not confined to the physiological properties which directly characterize the functions of the cerebral cortex. The specific traits of the type are also reflected in other systems of the organism. Thus, from the physiological point of view, type is a definite variation of the organism as a whole. It has been found (by M. Petrova et al.) that in animals with different types of nervous system changes and disturbances in the activity of the internal organs (kidneys, liver), i.e., pathological processes, do not proceed with equal ease and are characterized by certain peculiarities. It is true that the facts so far accumulated do not yet make it possible to predict exactly what way a particular pathological process will develop in various types of nervous system; however, the significance of the type characteristics as a factor which influences various functions of the organism under normal and pathological conditions can no longer be doubted.

Pharmacological and Endocrine Influences on Cerebral Hemispheres

Various pharmacological substances exert a strong influence on the functions of the cerebral cortex.

Of these pharmacological substances acting upon the nervous system bromides have long been known and widely used in medicine. Administration of certain doses of bromide accelerates elaboration of differentiations, retarded reflexes and other forms of internal inhibition, intensifying and concentrating it. This limits the irradiation of inhibition from its point of origin in the cerebral cortex, and phenomena of positive induction become more pronounced. Administration of bromides thus improves and makes more precise the equilibrium between the processes of excitation and inhibition. The weaker the process of internal inhibition, depending on the type of nervous system or functional disturbances of the cerebral hemispheres, the smaller the dose of bromide to be administered.

Caffeine intensifies the process of excitation in the cerebral hemispheres and is thus in a certain measure the physiological antagonist of bromide. Caffeine increases the excitability of the cortical cells, and the animal usually reacts to a stimulus more energetically and impetuously. Here, as in the case of bromide, the effect depends on the type of nervous system, the dose of caffeine and the functional state of the cerebral hemispheres. The weaker the nervous system, the smaller the dose that must be administered to obtain a useful effect.

The influence of endocrine disturbances on the higher nervous activity of man and animals has long been known in medicine. Hormones greatly influence so sensitive an organ as the cerebral hemispheres, and any change in the content of various hormones in the blood therefore markedly modifies the conditioned reflexes.

The influence exerted on the higher nervous activity of dogs by changes in the functioning of the sexual glands is now very well known. It has been found that increased activity of the sexual glands in female dogs during the heat and pregnancy produce changes in the cortical processes expressed in a fluctuation of the excitatory and inhibitory processes. A stable focus of excitation in the central nervous system during the performance of the sexual functions influences a number of conditioned reflexes evoking their external inhibition.

Numerous experiments have shown that castration of the male dogs weakens their cortical activity; for a certain period after the operation it is the inhibitory process that is particularly disturbed (M. Petrova). Some time later this is followed by periods of normal cortical work which are succeeded by periods of its chaotic work. Finally, the castrates that had the strong type of nervous system before the operation recover their normal efficiency. But a difficult nervous task—a delicate differentiation, a complex pattern, etc., imposed on a castrate—suffices to reproduce the pathological disorders in the activity of the cortex. In representatives of the weak types of nervous system the consequences of castration are even more pronounced.

Removal of the thyroid also results in marked disturbances in the activity of the cerebral cortex. Particularly striking results have been obtained in young, growing animals. In thyroidectomized puppies it is impossible to elaborate any alimentary conditioned reflexes whatever.

Functional Pathology of Cerebral Hemispheres

The work of Pavlov and of his school made it possible to induce functional disturbances of the cortical activity experimentally and invariably to obtain experimental neuroses.

The most effective method used in producing experimental neuroses is the overstrain of the basic processes in the cerebral cortex—excitation or inhibition. A neurosis can be obtained, for example, by overstraining the excitatory process as a result of a more or less protracted application of excessively strong stimuli, or by overstraining the inhibitory process; the latter can be achieved, for example, by the prolongation of the action of differentiating stimuli, or by the application of delicate differentiations, when the nonreinforced inhibitory stimulus is very close to the positive one. The emergence of a neurosis results in a so-called "breakdown" which may manifest itself in a predominance either of the excitatory or the inhibitory process. If the excitatory process predominates differentiations disappear; saliva—in experiments with alimentary conditioned reflexes—is secreted during the intervals between the conditioned stimuli; motor excitation appears; normal correlations between the intensity of the stimulus and the value of the conditioned reflex are deranged. If the inhibitory process predominates, positive conditioned reflexes weaken and disappear, drowsiness develops and the animal sleeps during the experiment. Various manifestations of the breakdown are also obtained through overstraining the *mobility* of the nervous processes, for example, by transforming the positive stimulus into an inhibitory, and at the same time by converting the inhibitory agent into a positive agent. Neurotic states may also arise as a result of interference with the normal work of the endocrine glands, i.e., in castration, thyroidectomy, etc. Neurosis is generally characterized by chaotic and inadequate behaviour.

Functional neuroses are easily obtained in representatives of the extreme types of nervous system, i.e., in representatives of the unequilibrated, impetuous type ("cholerics"), and, particularly, in animals with a weak inhibitory type of nervous system ("melancholics"). In the former the breakdown is mainly characterized by a predominance of excitation, while a disturbance of the already weak excitatory process and breakdowns with a still greater predominance of inhibition are characteristic of the latter. Thus it is the "extreme types" which are the chief "suppliers" of neuroses, although breakdowns of the normal higher nervous activity can, of course, also be produced by special measures in the strong—sanguine and phlegmatic—types.

As a rule, neuroses do not manifest themselves immediately after the application of pathogenic agents, but one or even several days later. The pathophysiological process, which underlies the chaotic and inadequate behaviour of the animal, is characterized by the following phenomena: 1) the cortical nerve cells weaken, i.e., their efficiency is reduced; 2) chronic hypnotic phases appear, sometimes persisting for months (paradoxical, ultra-paradoxical and other phases); 3) inertness of the nervous processes (more often of the excitatory process) or, on the contrary, excessive, pathological mobility of the cortical processes develops (especially of the excitatory process again). Pathological inertness takes the form of a reaction which arises extremely precipitately at the moment stimulation begins and during this stimulation is replaced by inhibition (picture of the so-called explosiveness, or "excitatory weakness").

The foregoing are the features peculiar to all experimentally induced neuroses.

Experimental neuroses in animals, evoking pathological deviations in the higher nervous activity, often lead to grave disorders of the functions of the internal organs.

For example, protracted changes in the bile-secreting function of the liver, disorders of diuresis, severe trophic lesions of the skin (M. Petrova, Bykov, Ussievich), changes in blood formation and in leukocytosis were observed in dogs under the action of factors leading to a breakdown of the higher nervous activity (Chernigovsky and Yaroshevsky).

In experiments with monkeys "day" was replaced by "night" and vice versa by artificial illumination and darkening; after the periodicity of the physiological functions in the monkeys was established at the given rhythm of alternation of "day" and "night" the elaborated pattern was deranged again and a new rhythm of alternation of light and darkness was introduced. This repeated strenuous exercise of the lability of the nervous processes, as a rule, produced hypertension and in some cases grave heart diseases in hamadryads and macacos. Prolonged and gradual rise in arterial pressure after such influences was also observed by a number of investigators in dogs. Protracted disorders of cardiac activity, sometimes approximating to the picture of infarction of the miocardium and even leading to death were easily provoked in cats by electric stimulation applied to their lips at the moment they were grasping pieces of meat (Kurtsin). But similar stimulation of the lips applied not at the moment of grasping food, did not evoke any cardiac disorders in them. It is interesting to note that pathological disturbances of cardiac activity, hypertension and breakdowns of the higher nervous activity almost invariably arise not immediately after the difficult tasks imposed on the nervous system, but some time later (for example, in the foregoing experiments with monkeys they arose 2 or 3 weeks after their return to the natural alternation of light and darkness).

CHAPTER 64

FUNCTIONS OF VARIOUS REGIONS OF CEREBRAL CORTEX

Methods of Studying Localization of Functions in Cerebral Cortex

One of the most important questions of the physiology of the cerebral hemispheres is the question of correlations between different functions of the cerebral cortex and the activity of its various structural formations, the question of the "adjustment of the dynamics to the structure" (Pavlov).

Until the seventies of last century it was almost universally recognized in physiology that different regions of the cerebral cortex were equivalent in their role (or, as it is sometimes said, equipotential). This view was based on the experiments of Flourens (between the twenties and thirties of the 19th century) who failed to disclose any distinctions in the consequences of extirpation of various parts of the cerebral hemispheres in pigeons. The situation changed when Hitzig and Fritsch demonstrated in 1870 that stimulation of definite regions of the cerebral cortex invariably led to contraction of certain muscle groups. Abundant experimental material accumulated already in the 19th century by Ferrier, Munk, Luciani, Ewald, Danilevsky, Monakow, Sherrington, Bekhterev and other researchers warrants the confident assertion that the result of stimulation or extirpation of various parts of the cerebral cortex depends on the region of the cortex to which the stimulated (or extirpated) part belongs.

The already mentioned ***method of stimulation*** consists in observing the reactions of the animals (usually dogs, cats and monkeys) during the application of stimuli to some, very definite parts of the cerebral cortex. Electrical stimulation is used for this purpose most frequently and sometimes certain chemical agents (for example, strychnine was used by Dusser de Barenne, absinth—by Orbeli). In some cases the cerebral cortex can also be stimulated in man when it is exposed during an operation on the brain: if local anaesthesia is used during the operation, it is possible to find out the sensations that arise in the patient and the movements he performs under delicate stimulations of different parts of the cerebral cortex (Penfield et al.).

The second method used in studying the specific functions of various parts of the cerebral cortex is the method of extirpation, i.e., removal of some part and subsequent thorough observation, for as long a time as possible, of the changes which manifest themselves in the behaviour of the animal. This is a coarse method; it is almost impossible to extirpate only a certain part of the cortex without injuring the neighbouring parts. The results of extirpation always depend not only on the removal of the extirpated part (or the part destroyed by coagulation), but also on stimulation of the intact parts of the cerebral cortex by the operative trauma. Furthermore, changes in the animal's condition after extirpation depend on the phenomena of compensation of functions, i.e., replacement of the functions of the removed cortical section by the activity of its other divisions, and secondary stimulation which is caused by the growth of the scar tissue. It would, therefore, be wrong to think that the changes observed after extirpation of a part of the cortex depend only on the removal of the given part; after removal of a part of the cortex the remaining parts of the cerebral cortex and the lower formations of the central nervous system exhibit somewhat different properties from those before the operation. Despite these defects, however, the method of extirpation has provided physiology with numerous valuable facts, since the most pronounced and constantly recurring changes in the state of the animal's condition following extirpation of a certain part of the brain largely depend on the disappearance of the functions of the removed part of the cerebral cortex.

Clinical observations are particularly important for understanding the localization of functions, since they make it possible to judge the role of the various divisions of the human cerebral cortex. The clinic ascertains the symptoms which invariably result from destruction of certain parts of the cortex (for example, after haemorrhage, thrombosis of the brain vessels, injuries or wounds, and surgical removal of a part of the cortex affected by a tumour).

Cyto-architectonic Areas of Cerebral Cortex

In 1874, V. Betz, a Kiev neurologist, discovered giant pyramidal cells, now bearing his name, in the anterior central convolution and came out with the statement that "each area of the cortex differs in structure from all other areas of the brain."*

It has now been established that different areas of the cerebral cortex are characterized by certain distinctions in the delicate structure of their cells (so-called *cyto-architectonics*) and by a different disposition and distribution of the nerve fibres (so-called *myelo-architectonics*). The investigations of Vogt, Brodmann, Economo and a number of scientific workers of the Moscow Institute of the Brain, headed by S. Sarkisov, disclosed about 50 various sections of the cerebral cortex (usually designated by numbers)—cortical cyto-architectonic areas, each of which differs from all other areas by delicate, sometimes almost imperceptible, peculiarities of form, density of disposition of the nerve cells and fibres and their distribution.

Consequences of Total Extirpation of Cerebral Cortex

Complete extirpation of the cerebral cortex in mammals (dogs) was first performed about 60 years ago by F. Goltz. After a series of successive operations Goltz left in the crania of the dogs only the medulla oblongata, the midbrain with the cerebellum, the corpora quadrigemina, the thalamus and part of the corpus striatum. These dogs were kept alive for about one year and a half by being very well cared for, artificially fed (the food was put into their mouths) and protected from any noxious agents. Deprived of the cerebral cortex they were unable to take food without assistance, to avoid injurious stimulations, to react to food and to answer to their names.

On the basis of these experiments Goltz (as was earlier done by Flourens on the basis of total extirpation of the cerebral hemispheres in birds) emphasized that removal of the cerebral cortex completely deprived the dog of its normal orientation in the environment. Interpreting his remarkable investigations in concepts and terms borrowed from psychology, Goltz stated that a decorticated dog lost the ability to understand, to recognize, to remember facts and objects. Only when the theory of conditioned reflexes was developed by Pavlov could the profound disturbances in the behaviour of animals arising after complete extirpation of the cerebral cortex be explained by the loss of all previously elaborated conditioned reflexes and the inability to elaborate new temporary connections.

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* Cited from L. Kukuyev's book *V. A. Betz*, 1950.

The removal of the cerebral cortex manifests itself not only in the disappearance of all the organism's reactions to signalling stimulations of the external environment, reactions acquired during the lifetime; disappearance of the conditioned reflexes, especially to interoceptive stimulations included in the pattern of a number of complex reflex acts, also modifies the activity of the internal organs. B. Bayandurov demonstrated (on birds and rodents) that removal of the higher division of the brain greatly influenced trophic activity, i.e., nutrition of the tissues, their supply with nutritive substances and the assimilation of these substances by the tissues. Removal of the cerebral hemispheres markedly retards the growth of young animals and changes their metabolism; normal daily periodicity is deranged (A. Slonim). Removal of the cortex makes impossible certain phenomena of compensation of functions which normally arise, for example, after the transplantation of tendons (p. 547), suturing of nerve trunks, and injuries to the spinal cord or cerebellum (E. Asratyan).

Experiments with complete extirpation of the cerebral cortex cannot reveal the peculiar properties of its various parts. This can be done best by experiments based on injuries to more or less limited areas of the cortex.

Consequences of Extirpation of Various Parts of Cerebral Cortex

Removal of different parts of the cerebral cortex produces different results. Removal of the occipital lobes results in the derangement of the animal's reactions to optic stimulations; removal of the temporal lobes deranges the reactions to acoustic stimulations; destruction of the cortical areas surrounding the cruciate fissure causes motor paralyses and disturbs the reactions to cutaneous stimulations. These observations gave rise to the thesis that the occipital lobes of the cerebral cortex were connected with the reception of optic stimulations; the temporal lobes, with acoustic stimulations; and the parietal lobes, with cutaneous stimulations (localization of smell, taste and particularly of pain sensibility and representation of the interoceptors in the cortex has not yet been adequately ascertained). Hence the concept of various *sensory* areas—visual, auditory, cutaneous, each of which occupies a certain part of the cerebral hemispheres: the visual zone is located in the occipital lobe; the auditory, in the temporal lobe; the cutaneous, in the parietal lobe.

Development of the method of studying conditioned reflexes, which made it possible to investigate the principal mechanisms of the higher nervous activity, enabled physiology to study objectively the consequences of extirpation of various parts of the cerebral cortex. This was accomplished by Pavlov and his school.

As before stated, the formations of the cerebral cortex, which receive impulses from the receptors, constituting the peripheral division of the given analyser, were designated by Pavlov as the cortical division (or cortical end) of each analyser (Fig. 267). Thus the cortical division of the visual analyser receives impulses caused by stimulation of the visual receptors (retina); the auditory analyser receives impulses from the auditory receptors; the interoceptive analyser, from the interoceptors, etc.

The material relating to the localization of functions should therefore be interpreted in the light of these concepts of analysers, i.e., of the cortical formations which analyse and synthesize the stimulations coming to the cortex.

Pavlov's investigations showed that if various parts of the cerebral cortex were extirpated in the dog, the nature of the disturbances of conditioned reflex activity in response to stimulation of different groups of receptors depended on the area of the cerebral cortex destroyed. Removal of the dog's occipital lobes disturbs the optic conditioned reflexes most; removal of the temporal lobes affects the acoustic conditioned reflexes; removal of *gyr. coronarius* and *ectosylvius* (Fig. 276), the conditioned reflexes to stimulation of the skin; and the removal of *gyr. sigmoideus*, the conditioned reflexes elaborated to the passive flexion of the extremities.

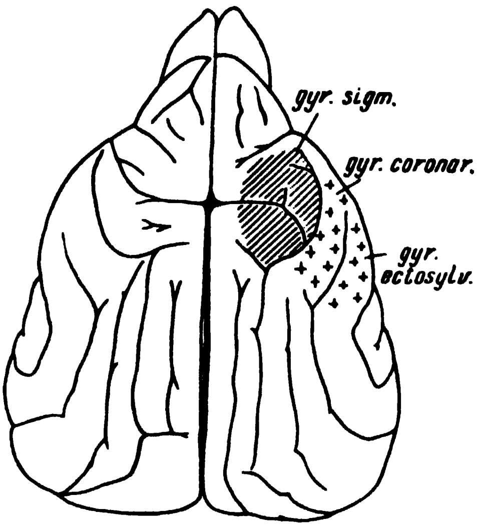

Fig. 276. Nuclear part of motor analyser (shaded) and of cutaneous analyser (crosses) in dog (after N. Krasnogorsky).

Disturbances of conditioned reflex activity resulting from destruction of the cortical division of any analyser are manifested in the following phenomena: during the first days after extirpation of a certain part of the cerebral cortex all, or almost all of the dog's conditioned reflexes disappear. (For the sake of simplicity let us assume that symmetrical cortical parts of the same name are removed in both hemispheres simultaneously.*) It is a result of the harsh "blow" upon the cerebral hemispheres, of the irritation caused by the operative trauma. But the unconditioned reflexes, such as salivation, winking, constriction of the pupil, jerking back the extremity in response to noxious stimulations, and the unconditioned orienting reflex to sudden, unusual stimulations, persist and can be observed almost immediately after the operation.

Several days after the operation conditioned reflexes to stimulation of all receptors recover, except those whose impulses were directed mainly to the extirpated areas of the cerebral cortex, or to parts injured by the operation; subsequently, if the damage to the cortex is not extensive, these conditioned reflexes also recover. For a very long time, however (and even for ever if the damage is substantial), the conditioned reflexes from these receptors alone remain generalized, and the differentiations disappear. Elaboration of conditioned (differentiating) inhibition to stimulations—not reinforced by an unconditioned reflex—of receptors connected with the damaged part of the brain is extremely impeded and is never fully possible. If the ability to elaborate differentiations is restored when the cortex is only slightly damaged, this ability is confined to differentiation of sharply differing agents. For example, after slight damage to the temporal zone it is possible to elaborate in the dog a differentiation between the sound of a metronome reinforced by food and the sound of a bell not reinforced by any unconditioned stimulus, but it proves impossible to obtain a differentiation between the different frequencies of the metronome; even when the cortical end of the auditory analyser is only slightly injured it is impossible to obtain a differentiation, say, between an ascending and descending series of tones; at the same time the ability to differentiate between considerably differing tones is retained.

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* Actually, the various parts of the cerebral cortex are usually removed in several stages with intervals of many days between them, since simultaneous exclusion of large areas of the cortex often leads to the animal's death in the first post-operative days.

Thus, dogs with the cortical division of some analyser greatly damaged retain the ability to elaborate conditioned reflexes to the stimulation of the peripheral division of the given analyser. But the greater the damage, the more affected the elaboration of the inhibitory process which underlies the analysis of various stimulations of the receptors; the higher synthesis, the ability to elaborate conditioned reflexes to complex stimuli and their differentiation, is also deranged.

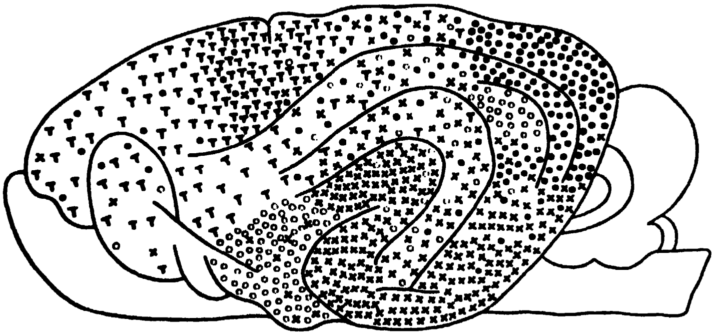

Fig. 277. Diagram of disposition of nuclear and peripheral parts of brain terminals of various analysers in cerebral hemispheres of the dog.

Black circles—cells of visual analyser; crosses—cells of auditory analyser; T-shaped symbols, cells of cutaneous and muscular analysers; white circles (according to data of several authors)—cells of taste analyser.

Fig. 277 shows the location of the brain ends of various analysers in the dog's cerebral cortex (these brain ends were previously called sensory zones). It shows that the cortical division of the cutaneous analyser is situated mainly in *gyr. coronarius* and *ectosylvius;* that of the motor analyser, in *gyr. sigmoideus*; of the visual analyser, in the occipital lobe of the cortex; of the auditory analyser, in the temporal lobe. It also shows that none of the cortical divisions of the various analysers in the dog represent strictly limited areas, but cover one another by their borders, and, consequently, overlap one another. This is testified to by the fact that dogs retain the conditioned reflexes to stimulations of the peripheral division of each analyser after extensive injuries to the cerebral cortex. Pavlov, therefore, considered each analyser to consist of a *nuclear* part and of a part *dispersed* over the cortex. The nuclear part represents a thorough and exact projection of all the elements of the peripheral receptor in the cortex and is indispensable to complex forms of conditioned reflex activity, such as elaboration of delicate differentiations, formation of complex conditioned reflexes, etc. As to the part of each analyser dispersed over the cortex, its cells are the "dispersed elements" which may be encountered far from the nuclear part (for example, cells receiving acoustic stimulations may be situated in the anterior parts of the cerebral hemispheres).

Pavlov conducted all his studies, relating to the consequences of extirpation of various parts of the brain, on dogs. Investigations carried out on other animals show that in the lower mammals, in rodents, and in birds, the localization of functions is less distinct. This is due to the slight structural distinctions between the various parts of the cerebral cortex in the lower animals. And this is why the data relating to rats in a certain measure coincide with the old data of Flourens who denied (on the basis of his experiments with birds) any localization of functions in the cerebral cortex. Rabbits, however, show distinctions between the functions of various parts of the cortex; this is testified to by the pictures of bio-electrical currents led off from different parts of the cerebral cortex (S. Sarkisov, M. Livanov).

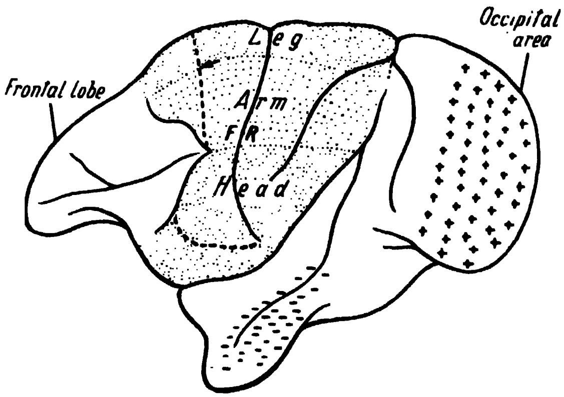

Fig. 278. Area of cortical representation of cutaneous and motor analysers (dots) showing projection for skin and muscles of arms, legs and head; areas of auditory analyser (dashes) and visual analysor (crosses) in monkey (macaco) (after Dusser de Barenne, with modifications).

The study of the effect of extirpation (and stimulation) of the cerebral cortex in monkeys shows that the localization of functions in the cortex of these animals is more pronounced than in the beasts of prey; but this localization is, apparently, more delicate in apes (the chimpanzee and the orangoutang) than in macacos and marmosets. This is expressed in the fact that in the former the areas of the brain occupied by the nuclear parts of the cortical divisions of various analysers are separated from each other (Fig. 278). It is possible that these areas are separated by such parts of the cortex which receive few axons from the cells of the thalamus, i.e., fibres transmitting excitation from the receptors to the cerebral cortex. In monkeys and in man the cells, to which impulses are conducted from each group of receptors along the axons ascending from the thalamus, are, apparently, dispersed less. There is also no doubt that in the course of the interconnected development of the functions and structure of the cerebral cortex the ability of the latter to form a fine mosaic of excited and inhibited points continuously increases. Indicative in this respect is the fact that in a number of rodents the action of a strong acoustic stimulus often leads to convulsive fits, which is not observed in mammals with a more developed cortex. In monkeys and, all the more, in man the compensation of functions of the damaged division of the cortex by the activity of the remaining, intact divisions is less pronounced than in dogs.

Functions, lost during the first days after injury to the cortical division of an analyser, recover to a certain extent even in man. It is still unknown, however, whether this is due to a real substitution of the functions of the extirpated part by the activity of the intact parts, or to the fact that with the lapse of time the pathological state in the intact parts of the cortex caused by the operation (haemorrhage or wound) disappears.

In apes and in man definite points of definite cortical areas correspond to each group of receptors. Different groups of receptors, for example, the tactile receptors of different areas of the skin and different fibres of the organ of Corti correspond to various groups of cells in the cortical divisions of their respective analysers. It has been stated that under the action of high tones, which stimulate the receptors at the base of the cochlea, bio-electric potentials arise in the cerebral cortex, mainly in the anterior part of Heschl's gyrus in the temporal lobe, where the cortical division of the auditory analyser is situated; but under the action of low tones which stimulate the receptors of the upper part of the cochlea, bio-electric potentials arise mainly in the part of this convolution situated closer to the occiput. With regard to the cortical division of the visual analyser it has been found that various sections of the occipital lobe of the brain (*area striata*) correspond to different squares of the retina.

Efferent Influences of Cerebral Cortex and Its Motor, Cutaneous and Interoceptive Analysers

The experiments which established that electric stimulation of certain areas of the dog's cerebral cortex invariably evoked contractions of various groups of muscles (Fritsch and Hitzig, 1870) played an important part in the development of the concepts of localization of functions. It had been found somewhat earlier that the loss of speech as a result of a cerebral haemorrhage in man was usually due to a lesion in a section of the third frontal convolution of the left hemisphere.

Almost simultaneously with the discovery of motor effects changes caused by electrical stimulation of the cerebral cortex (V. Danilevsky, N. Mislavsky, V. Bekhterev et al.) were also found in the heart rate, the blood pressure, the respiratory rhythm, and in the activity of other internal organs. These investigators, however, did not even concern themselves with the role of various parts of the cortex in *normal* regulation of all functions of the organism.

Prior to Pavlov the activity of the motor zone and the efferent functions of the cortex, in general, were erroneously interpreted as resulting from the excitation of special, always invariable cells of the cerebral cortex, of "centres" governing certain functions. The motor zone of the cortex (the cortical division of the motor analyser, to be exact) was regarded as an aggregate of "psychomotor centres." The question of the physiological mechanisms determining the role of the different parts of the brain in the various acts of the organism was actually disregarded and each activity was considered a result of excitation of a special "centre." But the question of *how* this "centre" had acquired the properties that determine the peculiar nature of its functions remained completely unsolved.

The theory of conditioned reflexes has disclosed the nervous mechanism by which the activity of the cerebral cortex ensures elaboration of ever new reflex processes according to the diverse agents that become conditioned stimuli. Hence the inevitable question: what is the mechanism of the very definite, more or less constant, reactions observed in response to stimulation of strictly fixed areas of the cerebral cortex?

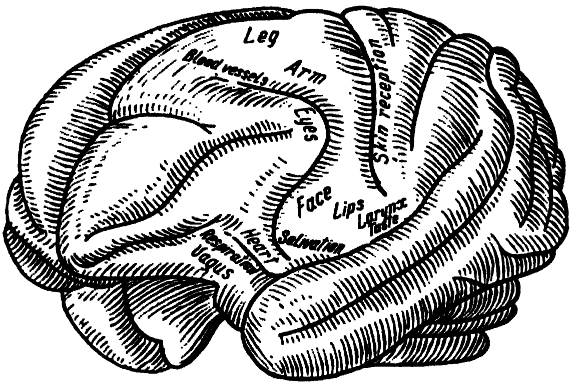

Fig. 279. Areas in cerebral cortex of monkey connected mainly with reactions to impulses from receptors of blood vessels, lungs, heart, vagus and area of motor and cutaneous analysers (after Bucy).

We already know that certain zones of the cerebral cortex are the cortical divisions of various analysers. We also know that in each muscle and in its tendons there is a large number of different receptors. Figures 279 and 280 show that in monkeys and in man the cortical areas, whose stimulation evokes contraction of various muscles, are concentrated mainly in the precentral convolution in front of the central (rolandic) fissure (area *IV*, Fig. 282). The cortical projection of the tactile sensibility of the skin is situated behind it, in the postcentral convolution (Fig. 280) For each section of the postcentral convolution, where the skin receptors of certain parts of the body are projected, there is (on the other side of the rolandic fissure) a corresponding section of the precentral convolution,

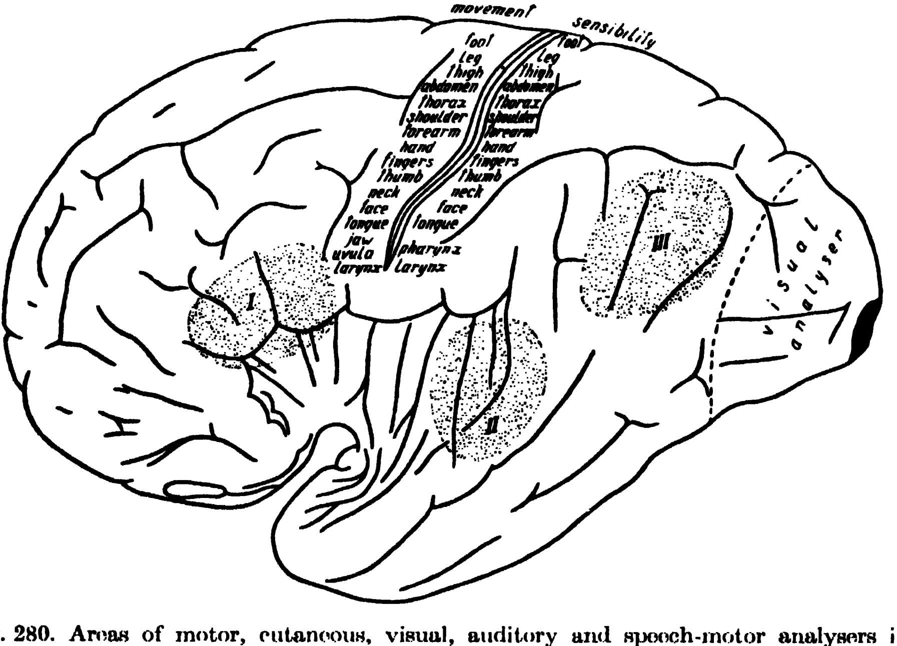

Fig. 280. Areas of motor, cutaneous, visual, auditory and speech-motor analysers in human cerebral cortex.

I—"Broca's centre" (area of speech-motor analyser); *II*—area, whose lesion causes sensory aphasia (auditory analyser); *III* area whose lesion leads to loss of ability to differentiate separate words. Area XVII (area striata) is blackened. Areas are not strictly delimited.

whose stimulation evokes contraction of the muscles of the *same* parts of the body. For example, the upper part of the postcentral convolution contains cells which receive impulses from the receptors of the leg and foot, whereas stimulation of the upper parts of the precentral convolution produces a strictly coordinated contraction of the muscles of the same parts of the body (Fig. 280) accompanied by a characteristic coordinated distribution of contraction and relaxation of the antagonistic muscles (Fig. 281).

The cortical localization of the representation of receptors of various skin areas in the postcentral concolution and the localization of the parts of the precentral convolution connected with different groups of muscles, can be graphically shown by a figure of a man drawn into these convolutions head downward (towards the base of the cranium) and feet upward (towards the fissure dividing the hemispheres). Since the cortical areas corresponding to the receptors of the face, especially to the receptors in the region of the mouth, are much larger than the areas corresponding to the lower extremities, such a figure, drawn into the cerebral cortex, must have an extremely large face and an unduly big mouth.

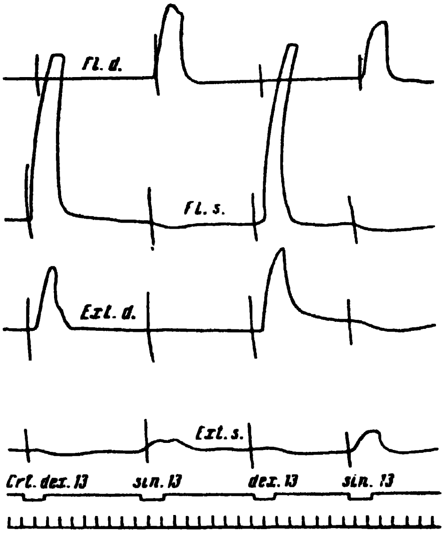

Fig. 281. Record of contraction of antagonistic muscles of both legs (mm. semitendinosi and mm. vasti crurales) under stimulation of motor zone of right (*Crt. dex. 13*) and left (*sin. 13*) cerebral hemispheres. Stimulations are indicated by fall of second line from bottom. Top to bottom: record of contractions of right flexor (*Fl.d.*), left flexor (*Fl.s.*), right extensor (*Ext.d.*) and left extensor (*Ext.s.*). Stimulation of cortex of right hemisphere produces flexion of left and extension of right paws. Stimulation of cortex of left hemisphere produces extension of left and flexion of right paws. Time interval—2 seconds (after A. Ukhtomsky).

Excitation from the interoceptors of the skeletal muscles continuously reaches the cerebral cortex. This is proved by the fact that *passive flexion of a limb can be converted into a conditioned stimulus for any function of the organism.* Accompanying the passive flexion of the hind leg (the dog's leg is flexed by the experimenter rather than by a contraction of the dog's muscles) by an introduction of acid, N. Krasnogorsky elaborated a defensive salivary reflex to this flexion. This conditioned reflex was subsequently differentiated from diverse stimulations of the skin which were not accompanied by an introduction of acid. When the cortical areas, which are mainly projections of the cutaneous analyser in the cortex (*gyr. coronarius* and *ectosylvius*, Fig. 276) were extirpated, all conditioned reflexes from the skin disappeared for a long time, while the conditioned reflex to the flexion of the extremity, i.e., caused by stimulation of the receptors of the muscles, persisted. But if the motor zone of the cortex (*gyr. sigmoideus*, Fig. 276) was removed, all conditioned reflexes elaborated to the flexion of the extremity disappeared, while conditioned reflexes from the skin were retained.

The aforesaid experiments carried out in Pavlov's laboratory have demonstrated that the motor zone of the cerebral cortex is the zone of cortical projection of the muscular receptors; it is the *motor analyser*.

In the light of these facts how are we to account for the invariable contraction of some muscle groups when certain parts of the motor analyser are stimulated?

From the moment the cerebral cortex in the child is fully formed and its normal functioning begins each muscular contraction generates impulses which are conducted from the receptors of the muscle to the part of the motor analyser where these receptors are projected. Consequently, excitation of each group of cells in the motor analyser always coincides in time with the contraction of the muscles whose receptors are projected in the given cortical cells. A temporary connection arises between the excitation of the receiving cells of the motor analyser in the cortex and the excitation of the motoneurons. In the given case these relations between the cerebral cortex and the motoneurons are, finally, fixed as definite morphological connections between the cerebral cortex and the motoneurons of the spinal cord by the fibres of the so-called *pyramidal* tract (Fig. 282); in rodents this tract is but very little developed; in dogs it can be distinctly traced only to the thoracic part of the spinal cord; in man it is developed most.

Cortical areas of eye muscles. It has been demonstrated that stimulation of area VIII of the cerebral cortex (Fig. 282) in the premotor area (see below, page 662) and area XVII situated in the neighbourhood of the cortical division of the visual analyser in the occipital part of the brain (Fig. 280) produces movements of the eyes. Various optic stimulations are always connected with various positions of the eyes fixed by contraction of the muscles of the eyeball. Consequently, when the eye muscles contract, not only impulses from the receptors of these muscles come to the cortex (to area VIII), but also impulses from the retina (to area XVII). As a result of this connection, which was at first elaborated, apparently, as a temporary connection, but was subsequently fixed in the phylogenesis, contraction of the eye muscles involves two cortical areas—the area of the visual analyser (area XVII) and that of the motor analyser (area VIII). In animals with well-developed ear muscles contraction of the latter similarly results from stimulation of the motor analyser and of the temporal area where the nuclear part of the auditory analyser is situated.

Pyramidal Tract and Extrapyramidal System

In man and the higher animals the area of the cerebral cortex whose stimulation by relatively weak currents evokes contraction of certain groups of muscles, i.e., area IV, has, according to Brodmann (Fig. 282), so-called giant pyramidal cells of Betz.

These Betz's cells (gigantic pyramids) project thick myelinated fibres of the pyramidal tract, which terminate at the cell bodies of the motoneurons of the anterior horns of the spinal cord (and at the nuclei of the trigeminal and facial nerves of the medulla oblongata). The axons of Betz's cells, consequently, form a direct pathway from the motor analyser to the motor nerve cells of the spinal cord. But Betz's cells in both hemispheres number approximately 70,000, whereas in both pyramidal tracts (right and left) on the level of the medulla oblongata there are about one million fibres (of which 60 per cent are myelinated and of different diameters, and 40 per cent unmyelinated). Thus, the pyramidal tract also contains axons of a mass of other nerve cells. Axons of cells from areas VI, V, III, I and

II of the cerebral cortex have been found in this tract in addition to those from area IV. The sites from which all the fibres of the pyramidal tract arise are not known as yet.

Most of the fibres of the pyramidal tract cross: they cross to the other side in the lower part of the medulla oblongata, i.e., the decussation of the pyramids, and then travel in the anterior lateral part of the spinal white matter (Fig. 247). Uncrossed fibres of the pyramidal tract extend in the posterior columns of the spinal cord; they also pass to the opposite side of the spinal cord on the level of the segments where they terminate at the cell bodies of the motoneurons. Thus, impulses from the cortex of each hemisphere are, in the main, transmitted to the motoneurons of the opposite side of the spinal cord. Stimulation of the cortical division of the motor analyser (in area IV) of the left hemisphere, therefore, provokes contraction of the muscles of the right side of the body.

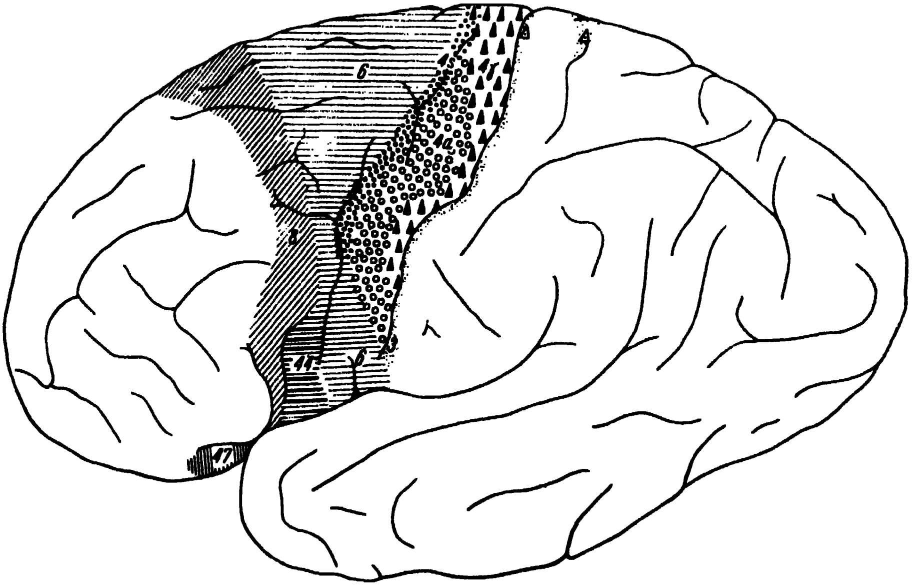

Fig. 282. Structure of motor analyser of chimpanzee.

Black triangles—area of Betz's cells (unshaded triangles indicate presence of dispersed Betz's cells also in these regions; *4s* "inhibitory area" described in motor analyser between areas IV and VI (after Bucy).

Efferent connections of cortex with internal organs. The efferent connections of the cerebral cortex are by no means confined to the skeletal muscles. The very fact that conditioned reflexes can be elaborated to any function of the organism shows that impulses from the cerebral cortex can reach *any* efferent neurons. As before stated, impulses from interoceptors also reach the cerebral cortex.

It is probable that the cortical structures receiving impulses from the receptors of the internal organs project descending axons which, through intermediate subcortical regions, conduct excitation from the cerebral cortex to the efferent neurons innervating these organs.

Fibres which extend from the cerebral cortex to the subthalamic region directly or through the basal ganglia and thalamus, have been described; from here, as is well known, the impulses are transmitted to the efferent neurons of the vegetative nervous system. The pyramidal tract possibly also includes direct pathways from the cortex to the neurons of the parasympathetic and sympathetic divisions of the vegetative nervous system.

We may suppose, at any rate, that the contraction of certain muscles simultaneously with the action of impulses from the receptors of these muscles upon the region of the motor analyser, continuously recurring through thousands of generations, has resulted in the formation of efferent pathways from the cortical projection of the muscular receptors (motor zone) to the motoneurons. It must be assumed there was a similar process in the formation of the connections between the cerebral cortex and the internal organs. Owing to this, the cortical structures receiving impulses from the internal organs—the blood vessels, heart, etc.—are the cortical areas which predominantly exert efferent influences on these organs. *Thus, the entire activity of the cortex, in the final analysis, apparently, results from the formation of temporary connections.* It is probable that in the course of historical development these connections may become hereditarily fixed in the form of morphologically differentiated nervous pathways between the cortex and the subcortical, subthalamic (and, possibly, bulbar and spinal) efferent neurons.

The cortical areas, whose electric stimulation evokes various effects mainly in the internal organs, include: areas VI, I, VII, VIII, and, above all, the so-called premotor zone (areas VI and VIII). Stimulation of area VI produces a number of vascular effects, modifies the heart rate, changes the size of the pupil and provokes movements of the intestines. The points from which a rise in blood pressure is obtained are often located apart from the points whose stimulation leads to a drop in blood pressure. Electric effects are recorded in area VIII during stimulation of the distal end of the vagus; direct stimulation of area VIII shows suspension of respiration and increased peristaltic movements of the intestines. The receptors of the afferent fibres of the vagus are, apparently, represented mainly in this area.

Removal of the premotor zone in the experiments of Bykov's collaborators resulted in the modification of the conditioned reflexes elaborated to the activity of the kidneys and gallbladder. This operation also deranged water excretion when too much water was consumed (A. Ginetsinsky). It has not been shown, however, that the premotor zone is the *only* site where all interoceptors are projected and correspondingly the only site where the cortex gives rise to descending fibres which connect it with the efferent innervation of the internal organs. At the same time there is no doubt that this area of the brain is of essential importance for the reaction to interoceptive impulses.

Extrapyramidal system and premotor zone. Stimulation of the premotor zone (area VI, Fig. 282) not only evokes changes in the activity of the internal organs, but also leads to motor effects which differ from the results of stimulation of the motor zone in that 1) they arise only when stronger stimulations are used; 2) they result not in the contraction of individual muscles, but in more general movements of the limbs, trunk, or head; 3) they largely (but not fully) disappear after removal of the motor zone (precentral convolution, i.e., area IV).

Experiments performed on monkeys have shown (and observations on the consequences of brain lesions in man have confirmed it) that removal of area IV results in muscular paralysis on the side of the body opposite to that where these parts of the brain have been removed. The extremity gradually recovers its movements, but the fine movements of the digits are paralyzed for ever (the extensive representation of the digital muscles in the cortical division of the motor analyser should be recalled in this connection).

When the premotor zone is removed, the muscles generally retain their ability to contract, but the ability to effect muscular contractions requiring delicate differentiations between various motor conditioned reflexes is lost, especially in the higher mammals; all movements therefore become extremely "awkward," and the newly elaborated motor conditioned reflexes are unstable.

Unlike atonia which develops in monkeys after removal of the motor zone, removal of the premotor zone increases the tone of a number of muscle groups which forces the anterior extremities and digits to flex (Fig. 259).

Connections of extrapyramidal system. Connecting fibres run from area VI to area IV (motor zone); in addition, there is a vast system of connections between the cortex and the efferent neurons through the subcortical ganglia and nuclei of the diencephalon and midbrain. The entire system connecting the cerebral cortex with the motor efferent neurons through the efferent nuclei of the brain outside the pyramidal tract (including the premotor zone of the cortex), is therefore called the *extrapyramidal system.* It includes: a) the premotor zone; b) the corpus striatum (*nucl. caudatus, putamen, globus pallidus);* c) the substantia nigra, the red nucleus and *corpus luyisi* of the midbrain. The cerebellum must probably also be included in this system. The connections of the extrapyramidal system are schematically shown in Fig. 261.

In the cerebral cortex there are certain sections (in the motor and premotor zones) whose stimulation leads to inhibition of motor effects evoked by stimulation of other sections of the brain (sections 4*s* in Fig. 282). It is probable that impulses from these "inhibitory sections" of the cortex, passing through *nucleus caudatus* and *globus pallidus,* reach the thalamus, in which responsive impulses arise again, proceed to the cortex and produce inhibition in it.

Normally the functioning of the structures of the extrapyramidal system always depends on the activity of the cerebral cortex. The existence of fibres extending from the premotor zone to *globus pallidus* and *nucl. caudatus* is beyond any doubt. It is also possible that there are fibres extending from the cerebral cortex to the putamen. Therefore, the results of injuries to the strial system are partly accounted for by the exclusion of the structures which conduct impulses from the premotor zone of the cerebral cortex to the lower centres.

A characteristic symptom of the lesion of the globus pallidus (especially when the *subst. nigra* and *corpus luyisi* are simultaneously affected) is tremor or torpidity of the muscles often due to considerable inertness of the basic nervous processes—excitation and inhibition. This entire symptom-complex is called Parkinsonism and is often observed after encephalitis. Lesions of the striopallidal system often also show so-called *hyperkinesis*—forced movements which do not produce a full motor effect, cannot be inhibited by the activity of the cortex and are expressed in tremor, convulsive contraction of a number of muscles (chorea) and peculiar vermicular movements of the limbs (athetosis).

Electric Phenomena in Cerebral Hemispheres

Electric phenomena in brain. Studies of the electric potentials conditioned by the activity of the brain have lately become very important in the investigation of this activity.

As far back as the seventies of last century Danilevsky described the modification of electric potentials mainly of the posterior divisions of the cerebral cortex occurring during acoustic stimulation, and of the anterior divisions of the cortex during cutaneous stimulation. Electrophysiological investigations first assumed importance in the elaboration of concepts relating to localization of functions. Subsequently, this trend was developed in the works of V. Bekhterev and his collaborators, and particularly in modern researches both in the U.S.S.R. (S. Sarkisov, M. Livanov, A. Kogan et al.) and abroad.

Danilevsky also indicated there were waves of electric potentials in the cerebral cortex even when no stimulations were applied to the receptors or afferent nerves. This was further elaborated by Sechenov in 1882; he discovered rhythmic electric waves in the frog's medulla oblongata which not only arose in the absence of any stimulation of the receptors, but were even suppressed by strong stimulations. Designating the above-mentioned waves as "spontaneous," since they arose "without apparent cause," Sechenov emphasized that this term was in no way used by him to indicate the nature of the phenomenon, but only the explosive character of its manifestation; this statement is also important for present-day physiology since some modern researchers regard the rhythm of bio-electric currents in the brain as a manifestation of its permanent properties, irrespective of the conditions of existence and development of the organism as a whole.

The use by V. Pravdich-Neminsky (1925) of a highly mobile string galvanometer instead of the inert mirror galvanometer formerly used by investigators was an important event in the investigation of electric phenomena in the cerebral hemispheres. By leading off bio-electric currents from the cerebral cortex of mammals to a string galvanometer, Pravdich-Neminsky gave a precise description of the electrical waves in the cortex (which he named the waves of the first and second order) now usually designated as alpha and beta waves. Later, in 1929, the German psychiatrist G. Berger began to investigate the electric activity of the human cerebral cortex by leading off bio-electric currents from the brain to a galvanometer of low inertness through an amplifier.

The recording of electric phenomena in the human cerebral cortex through the coverings of the cranium and skin has made it possible to extend the studies of electric phenomena in the higher division of the central nervous system. The recording of electric phenomena in the brain, so-called electro-encephalography, is becoming as important in the clinic of cerebral lesions as electrocardiography is in the clinic of heart diseases.

Electro-encephalography. The cerebral cortex of man and animals exhibits rhythmically arising electric potentials. They are observed at complete rest and during sleep (Fig. 283, on the right) and disappear only in deep narcosis.

Alpha and beta waves are the first to be distinguished in the electric activity of the human cerebral cortex. Alpha waves (Fig. 283, *a)* are oscillations of potentials with a frequency of about 10 per second (9 to 12) and with a relatively high voltage (about 500 microvolts). They are connected mainly with the activity of the occipital (visual) zone of the cortex and disappear under the action of illumination, when the eyes are fixed on a certain object, under intense stimulations of other receptors, when complex motor acts are effected, when a focus of excitation arises in the brain, in the course of solving mathematical problems, etc. This is the so-called depression of the alpha-rhythm (Fig. 283 on the right).

Beta waves are small electric oscillations often superposed on the alpha waves (Fig. 283, *b)* and especially clearly seen in electro-encephalograms when the alpha waves are depressed.

In *deep* sleep alpha waves are succeeded by delta waves, i.e., by still slower, longer and less frequent oscillations (4 to 5 oscillations per minute) of the electric potential of the cortex (Fig. 283, on the right). Delta waves emerge not only in sleep, but also in grave pathological disturbances of the brain, in the presence of tumours and in epilepsy (Fig. 283, *e*).

Studies of electric potentials of the brain are also important for the characteristics of conditioned reflex activity. It has been demonstrated (M. Livanov) that if stimulation of the visual analyser of the rabbit, applied in a certain rhythm, is accompanied by electric stimulation of the skin applied in the same rhythm, under the isolated action of flashes of light the bio-electric currents in the region of the motor analyser assume the rhythm of the optic stimulations applied to the eye. While a conditioned reflex to the flashes of a light is still in the process of elaboration, bio-electric currents isorhythmic with the flashes are recorded in the motor analyser even in the absence of the flashes, probably because of the experimental conditions which are transformed into a conditioned stimulus. But after the elaboration of a stable conditioned motor reflex rhythmic currents arise in the motor analyser only in response to signalling optic stimulations.

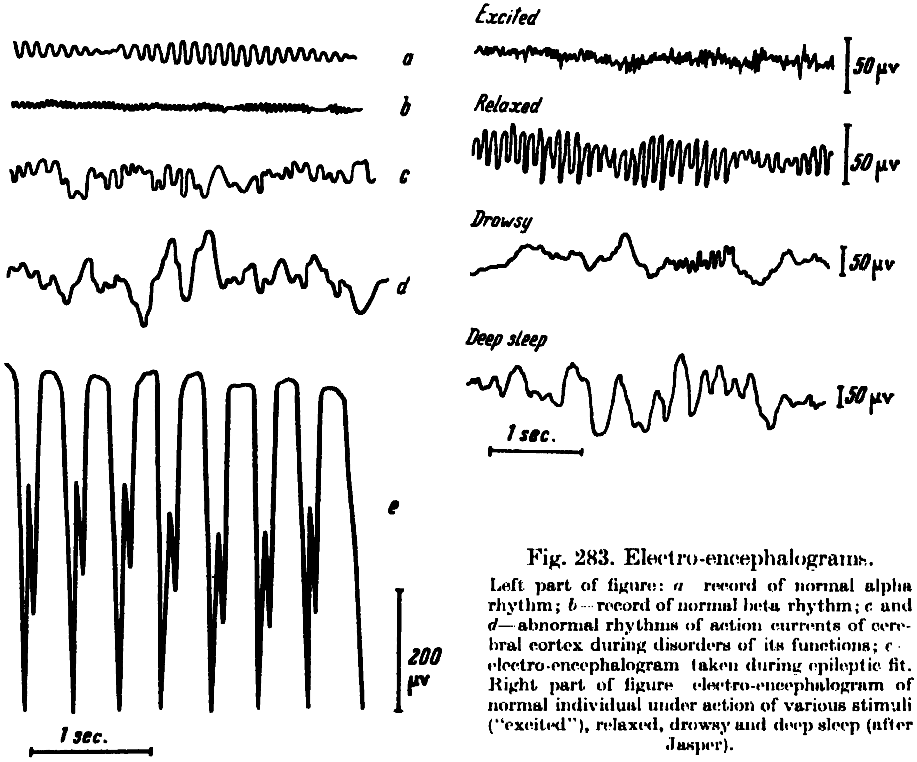

Fig. 283. Electro-encephalograms.

Left part of figure: *a* record of normal alpha rhythm; *b*—record of normal beta rhythm; *c* and *d*—abnormal rhythms of action currents of cerebral cortex during disorders of its functions; *e* electro-encephalogram taken during epileptic fit. Right part of figure electro-encephalogram of normal individual under action of various stimuli ("excited"), relaxed, drowsy and deep sleep (after Jasper).

It has also been demonstrated that by combining indifferent stimuli (indifferent as regards their influence on the bio-electric currents in the brain) with agents which depress the alpha rhythm, it is possible, owing to the elaboration of a conditioned reflex, subsequently also to obtain such a depression under the action of the previously indifferent stimuli.

Temporary connections between two groups of cortical cells are also elaborated under their simultaneous direct stimulation by electrodes applied to various areas of the cerebral cortex (Livanov).

CHAPTER 65

CHARACTERISTIC FEATURES OF HIGHER NERVOUS ACTIVITY IN MAN

Concept of First and Second Systems of Signals of Reality

In his teaching on the interconnected first and second systems of signals of reality Pavlov indicated the ways to extend the physiological, natural-scientific analysis to the knowledge of the peculiar functions of the human cerebral cortex.

In addition to the mechanisms governing the activity of the cerebral cortex, common to man and the higher animals, man has other specific functions of the cerebral hemispheres which have arisen in the process of historical development of human society and distinguish man from all other animals. Pavlov believed that the specific properties acquired by the human cerebral cortex depended on the new way of interaction with the environment which arose in the course of human labour activity and was expressed in speech. "... It is precisely speech which has made us human ...,"* Pavlov stated. Consequently, only by analysing the physiological mechanisms of speech, only by studying the reactions which arise because of the emergence of speech is it possible to get an insight into the specific features which distinguish the higher nervous activity of man from that of animals.

"In the animal," Pavlov wrote, "reality is signalized almost exclusively by stimulations and by the traces they leave in the cerebral hemispheres, which come directly to the special cells of the visual, auditory or other receptors of the organism. This is what we, too, possess as impressions, sensations and notions of the natural world around us.... This is the first system of signals of reality common to man and animals. But speech constitutes a second signalling system of reality, which is peculiarly ours, being the signal of the first signals."**

The action of various objects and phenomena of the surrounding world upon the cerebral cortex through stimulation of the receptors is always a concrete signal of reality. This is the first system of signals of reality. But speech, according to Pavlov, represents "... especially and primarily kinesthetic*** stimulations which proceed from the speech organs to the cortex...." These stimulations constitute a set of second signals, the signals of signals. "They represent an abstraction from reality and make possible the forming of generalizations; this constitutes our extra, *specially human, higher mentality*, which creates an empiricism general to all men and then, in the end, science, the instrument of the higher orientation of man in the surrounding world and in himself."****

Any agent acting upon a receptor becomes a signal because of the activity of the higher division of the central nervous system. The first signalling system implies the entire activity of the cortex which determines the conversion of the given stimuli into signals of various activities of the organism. The second signalling system implies the entire peculiarly human cortical activity which ensures speech signalization between men, establishment of connections between objects (phenomena) and words by which they are designated, and accomplishment of various acts resulting from the influence of verbal stimuli.

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* I. Pavlov, *Complete Works*, Vol. III, Book 2, p. 336.

** *Ibid.*, pp. 335-36.

*** Kinesthetic stimulations are those which proceed from the receptors of the muscles, in the given case, the muscles of the speech organs—tongue, larynx, lips, cheeks. (*Author's note.*)

**** I. Pavlov, *Complete Works*, Vol. III, Book 2, pp. 232-33.

Formation of Second Signalling System

Verbal designations replace the action of agents of the first signalling system and enable the organism to react not only to the direct influence of various real objects and phenomena, but also to their verbal designations. Connections between the verbal signals and the real stimuli are established in accordance with the laws of formation of conditioned reflexes, in accordance with the laws of elaboration of temporary connections. At the same time the second signalling system always functions in connection with the first system, and its activity cannot be considered apart from the reactions of the organism to the first system of signals.

The utterance of syllables and words stimulates the receptors of the speech muscles, i.e., the muscles of the tongue, lips, cheeks and larynx. These stimulations enter the central nervous system, and upon reaching the cortex excite certain cellular groups of the cortical division of the motor—kinesthetic—analyser. The cortical neurons of this analyser connected with the receptors of the speech muscles play so important a part that in the aggregate they should be properly called the cortical division of the speech motor analyser. It is represented mainly by the area of the frontal convolution of the cortex of the left hemisphere (in right-handed people), which was previously described as the "motor centre of speech" (Fig. 280) discovered by Broca as far back as the sixties of last century (Broca's centre).

When various syllables and words are pronounced, different kinesthetic stimulations come from the receptors of the speech organs to the speech motor analyser. Excitation of the cortical cells during the pronunciation of words always coincides in time with acoustic stimulations produced by the sound of these words and with visual, tactile, taste and other stimulations resulting from the direct influence of the object (or action), designated by the pronounced words, upon the first signalling system. For example, when little children pronounce (and simultaneously hear) the word "milk," they associate it with the sight, smell and taste of milk; when they pronounce and hear the word "mamma," they associate it with a number of visual, tactile, olfactory and acoustic stimulations, coming from this definite person. The stimulation produced in the cerebral cortex as each word is pronounced, is combined, according to the principle of elaboration of temporary connections, with the stimulations of the first signalling system produced by the objects designated by each word. Thus, the words turn into signals of the objects which they designated.

By the end of the second year of life the vocabulary of a normal child consists of more than 200 words, and already at this time the child shows a grammatical connection between the words and combines them into sentences. This is due to the well-developed synthesizing activity of the cerebral cortex, which ensures the combination of syllables and words signalizing various objects and phenomena (for example, "give me," etc.)

into most elementary sentences. The child mainly imitates the speech of the adults, which is of prime importance at this time.

The entire activity of the second signalling system, the uttering of words and all the reactions to speech signals are elaborated during the lifetime by the formation of speech conditioned reflexes resulting from the synthesizing and analysing activity of the human brain. Pavlov stated: "... speech is as real a conditioned stimulus to man as all other stimuli which are common to man and animals; but at the same time, it is unlike other stimuli, that it can be neither quantitatively nor qualitatively compared in this respect with the conditioned stimuli of animals. Owing to the entire preceding life of the adult, speech is connected with all external and internal stimulations coming to the cerebral hemispheres, signalizes all of them, replaces them and, therefore, can provoke all the actions and responses of the organism conditioned by those stimulations."*

In man any agent may be connected with verbal stimulation. Ivanov-Smolensky's studies of children from eight to ten years of age demonstrated that if some concrete agent (for example, the sound of a bell) was made a conditioned stimulus of a certain motor reaction (pressing a balloon or jerking the hand away when the skin was stimulated by electricity), the mere utterance of the word "bell" or this word shown in writing at once produced the same reaction without any reinforcement. Contrariwise, if the reaction was elaborated to the word "bell," the sound of the bell (or the written word "bell") produced the same reaction as the spoken word "bell." As indicated in Pavlov's foregoing statement, when speech forms a connection with a concrete stimulus it signalizes and replaces it. This is why the word "bell" produces the same effect as the real sound of a bell. Moreover, we see that there is no fundamental difference between words heard, read or spoken: the reaction evoked by verbal stimulation also manifests itself when the given word is seen in writing.

Verbal stimulations can signalize not only actions, but also their inhibition: if, for example, a green light is reinforced by an unconditioned stimulus, while a differentiation has been elaborated to a red light, the words "red light" will evoke no reaction. Whenever speech replaces concrete stimulation (for example, when the word "light" replaces the flash of an electric bulb), the connections between the cortical excitation, evoked by the verbal signal, and that which arises from stimulation of the receptors by the agent designated by this word are coupled.

Observation of children has established the fact that stimuli of the first signalling system can also be converted into signals of the second order when combined with a reaction evoked by a verbal stimulus. For example, a child is told to do something (to press a balloon connected with a recording apparatus). Before telling the child to do it the experimenter applies some stimulus (for example, a flash of an electric bulb) which was previously indifferent in relation to the accomplishment of the task. After several such combinations the child presses the balloon before it is told to do so merely under the action of the agent of the first signalling system, i.e., the flash of the electric bulb. In this case speech, i.e., the stimulus of the second signalling system, replaces the unconditioned stimulus, while agents coinciding in time with the verbal stimulus (flashes of the electric bulb) and previously included only in the activity of the first signalling system, become signals of this verbal stimulus.

Verbal designations of various influences upon the organism evoke the same changes in the work of the internal organs as the unconditioned stimuli designated by them, or stimuli of the first signalling system of reality. For example, the words "I ring the bell" evoke the same vascular reaction as was produced by the sound of the bell itself (Fig 284), if the latter, being combined with a pain stimulation, was previously transformed into a signal of this stimulation.

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* *Ibid.*, Vol. IV, pp. 428-29.

In man numerous agents of the first signalling system acquire certain verbal designations, thus evoking the activity of the second signalling system. As the second signalling system begins to be formed this is due to the fact that stimulation of receptors, which arises when each word is pronounced and heard, is accompanied or, one may say, reinforced by the direct action of the agent designated by the given word. Subsequently, many new words acquire their meaning because of their combination with the already elaborated verbal designations of concrete objects, and not with the direct action of the latter on the receptors. Only due to such chains do all objects (phenomena), whose direct action we have never experienced, become signals for us in the form of definite words; owing to these chains previously unknown words become signals of certain objects through the medium of other words, which had earlier become signals of definite objects and phenomena. Such chains may be very complex and have many links, each of which is based on the combination of different speech signals. The initial link is always based on the combination of the action of speech stimulation with a concrete agent of the external world.

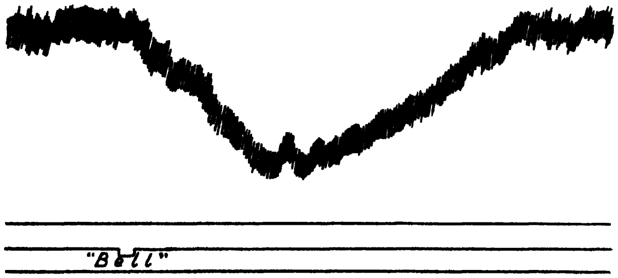

Fig. 284. Constriction of blood vessels in arm (fall in plethysmogram) at the words "I ring the bell" (mark *bell*). Prior to this actual sound of bell was transformed into stimulus producing conditioned reflex constriction of blood vessels due to combination of sound of bell with pain stimulus (heating of certain skin area with thermode at temperature of 60° C) (after A. Pshonik).

Second Signalling System and Abstraction from Reality

No word (if considered as a physical stimulus, as a complex of sounds, or a complex of lines and symbols forming its letters) has, as regards its properties, any permanent relation to the object it designates. Consequently, any verbal designation of an object implies abstraction from its concrete properties.

General natural stimuli of the first signalling system, i.e., stimuli common to man and animals can act upon us only in the presence of an agent of the external or internal environment which evokes them: there can be no thermal stimulation in the absence of a source of heat, and no peal of thunder without an electrical discharge in the atmosphere. If the highest orientation of the animals in the surrounding world is to be designated as thinking, then it is invariably and exclusively concrete, object thinking, conditioned, temporary connections with agents acting at the given moment upon the organism (and connections with the immediate traces of various agents).

Verbal designations may be reproduced in the absence of the object the given word designates. Words can be reproduced not by being uttered, but also by being written or by being thought (the latter occurs when they are not spoken or revealed in other motor acts).

The second signalling system arises and exists as a means of intercourse between men in their labour activity. This is due to the fact that one man may be influenced by verbal designations of agents which at the given moment directly act upon another man evoking a speech reaction in him; owing to the existence of a written language, we can be influenced by agents which acted, even in very remote times, upon the author of the texts we read. Furthermore, due to varied temporary connections with different words, connections which arise depending on the results produced by the agents designated by them, the words uttered or heard by us continuously lead to the emergence of new reactions within the second signalling system again. In the foregoing example the word "bell" made the child jerk the hand away, reach for a candy, etc., depending on the signal meaning of the bell.

Since each word, designating a real object, is in itself deprived of the concrete properties of the given object, man is able to orient himself not only in his immediate environment. Everything designated as recollections, as orientation in coming events (beyond the reinforcement of the first signals by the reflex on the basis of which it was elaborated), and all of science (see Pavlov's statement above, p. 668) are based on the fact that speech is a signal of reality, a signal which arose under conditions of definite, concrete human intercourse, but at the same time deprived of the concrete properties of the objetcs it designates.

PART XIV

ANALYSERS (SENSE ORGANS)

CHAPTER 66

GENERAL CHARACTERISTICS OF ANALYSERS

Subjective Character of Pre-Pavlovian Physiology of Sense Organs

Prior to Pavlov the theory of the sense organs was based largely on materials obtained from subjective observations on human sensations and notions. It is true, important data pertaining to the structure of the receptor apparatuses of the sense organs were obtained. The physical aspect of the processes going on in some of them (especially in the eye) was profoundly and extensively investigated, and in this respect this branch of physiology was, undoubtedly, developed most. As to the strictly physiological aspect, as Pavlov pointed out, only elementary facts were established.

The physiology of the sense organs was an arena of the bitter struggle between the materialist and idealist world outlooks, a struggle concentrated around questions relating to the specific nature of the activity of the sense organs. Owing to its specific structure, each sense organ normally reacts only to one form of stimulation: light waves are the specific or adequate stimuli for the eye; sound waves, for the ear; certain chemical substances, for the organs of smell and taste, etc. But at the same time it is well known that certain inadequate stimuli (mechanical stimulation in the form of a blow, push or pressure, application of an electric current, or of any other strong stimulus to the given organ) produce the sensation of light and colours when acting upon the eye and the sensation of sound when acting upon the ear. In this case, however, the sensations are elementary and deprived of any qualitative nuances in which normal sensations are so rich. They may result from stimulation not only of the end-organ, but also of the nerve trunk. For example, transection of the optic nerve during an operation produces a sensation of light or glare without any visual image.

These functional qualities of the sense organs, pointed out by the German physiologist Johannes Müller (1840), gave him ground to formulate the so-called law of specific irritability. According to this law, the qualities of sensations do not depend on the nature of the stimulus, but are fully determined by the specific energy inherent in the sensory systems, which was regarded by Müller as an inborn, invariable "vital property."

Proceeding from the incorrect vitalistic approach to the activity of the sense organs, Müller came to the idealist conclusion of the unknowability of the external world, since, according to his point of view, it is only the properties and states of the sense organs themselves which reach our conscience through the sense organs, and not the properties and states of the objects of the external world. These fundamentally wrong conceptions of Müller concerning the activity of the sense organs were caught up by all agnostics and idealists as a "physiological" substantiation of the unknowability of the objective world.

Criticizing the fundamental principles of idealism which denies the objectivity and knowability of the external world, V. I. Lenin characterized Müller's "physiological idealism" as follows: "The idealism of this physiologist consisted in the fact that in investigating the mechanism of our sense organs in relation to sensations and showing, for example, that the sensation of light was produced by the action of various stimuli on the eye, he was inclined to deny on this basis that our sensations were images of objective reality."* Characterizing idealist philosophy, Lenin stated: "The sophism of idealist philosophy consists in the fact that it regards sensation as being not the connection between consciousness and the external world, but a fence, a wall, separating consciousness from the external world—not as an image of the external phenomenon corresponding to the sensation, but as the 'sole entity'."**

According to Lenin's theory of reverberation, the external world, as an objective reality existing outside and independent of consciousness, is the source of sensations. Sensations are, according to Lenin, the subjective images of objective things. This means that sensations, resulting from the influence of the external world on the sense organs of man, possess specific qualitative properties and a subjective character, at the same time reflecting the objective properties of things.

Alien to the ideas of evolutionary development Müller overlooked the fact that the specific functional properties of the sense organs were the result of a long biological evolution towards a fuller adaptation of the organism to the conditions of its existence, towards more delicate and differentiated reactions to various influences of the external world. Far from preventing knowledge of the external world the specific nature of the activity of the sense organs therefore ensures a more exact reflection and synthesis of its phenomena. The more pronounced the specific nature of the activity of a sense organ, the more differentiated its reaction, the more exactly is the objective material world reflected in the sensations.

S. Vavilov, outstanding physicist of our time, convincingly showed exactly how in the course of a long evolution the eye adapted itself to the illumination created on the earth by the sun: "One cannot comprehend the eye without knowing the properties of the sun. On the contrary, it is the properties of the sun which make it possible theoretically to outline the specific features of the eye, as they should actually be, without knowing them in advance."***

Not only the sense organs react specifically. The activity of any tissue, any organ is specific. The specific nature of any activity is not something given beforehand and for ever, but a result of a long evolutionary process.

Another idealist trend in the physiology of the sense organs is the conception of psychophysical parallelism. This trend found particular expression in the works of the German physiologist Ewald Hering. According to him, mental and physiological (nervous) processes are two different series of phenomena not connected by causality, but only by simultaneity of phenomena, by their parallel development. Hering formulated this proposition as follows: "There is no movement in the soul without movement in the brain, and vice versa."

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* V. I. Lenin, *Works*, Vol. XIV, p. 290.

** *Ibid.*, p. 40.

*** S. Vavilov, *The Eye and the Sun*, 5th ed., 1950, p. 122.

Closely connected with this proposition was Hering's assertion that the subjective method of introspection, i.e., of observing one's own mental phenomena, was the principal method of studying the functions of the brain since, according to him, we were able to judge of the nervous processes in the brain only by our own sensations. Accordingly, Hering based the study of the functions of the sense organs on the method of introspection, on the analysis of subjective mental states.

Criticizing the old physiology of the sense organs with its subjective methods of studying sensations, Pavlov justly pointed out: "...in the doctrine on sensations and ideas resulting from stimulation of these organs, only elementary facts have been established, despite the skill and keenness displayed by investigators in this field."*

Pavlov's Teaching on Analysers

Pavlov remade the entire physiology of the sense organs and provided it with a strictly scientific, materialist base in the form of his broad biological teaching on analysers. This teaching, directly connected with the physiology of the brain, made it possible to pass from a purely subjective interpretation of sensations to their objective and strictly scientific study. The activity of the higher division of the nervous system was considered by Pavlov from the aspect of two basic nervous mechanisms: the mechanism of temporary connections and the mechanism of analysers inseparably connected with the processes of synthesis.

The peripheral division of an analyser is a receptor apparatus responding only to a certain kind of stimulation and representing a specialized transformer of the external energy into a nervous process. The function of the conductive division is transmission of nervous excitation from the receptor apparatus to the intermediate centres of the spinal cord and brain stem, where a reflex connection with various efferent systems can be effected and where interaction between impulses from various receptor apparatuses belonging to different analysers takes place.

The cerebral, or cortical division is the higher division of an analyser. Here nervous excitation acquires new properties and is converted into sensations.** Here, too, the highest and most delicate analysis occurs. This analysis is indissolubly bound up with synthesis, which, in the end, determines the perfect equilibration of the organism with the external environment. The signals coming from various analysers are also synthesized and treated here.

Hence, it is clear that the physiology of the sense organs should not be approached as a physiology of the peripheral receptors alone, apart from the central nervous mechanism. Such artificial division has resulted, as before stated, in a number of erroneous conceptions and has greatly impeded the establishment of the general laws governing the analysing and synthesizing activity of the cerebral cortex.

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* I. Pavlov, *Complete Works*, Vol. III, Book 1, p. 121.

** By the term "sensation" we imply the aggregate of certain physiological processes.

The peripheral division of the analysers includes all sense organs, and among them special receptor apparatuses, situated in the internal organs and muscles.

Evolution of Receptor Apparatuses

The process of evolutionary development of receptor apparatuses in lower animals is characterized by the formation of special sensory cells on the surface of the organism which comes in contact with the external environment. These primitive receptor cells reveal the ability to react to various direct stimuli (mechanical, chemical and thermal).

In the process of further development the receptor cells dispersed over the entire surface of the body begin to concentrate in definite areas, for example, around the mouth, or on the tentacles, as, for example, in the medusae. At the same time the receptor cells become differentiated functionally. The cells around the mouth specialize in responding to chemical stimuli. Aggregations of cells on the tentacles become particularly sensitive to mechanical stimuli. Thus, the initial elementary forms of reception give rise to new differentiated forms specially adapted to certain stimuli. Differentiated receptor cells normally respond with excitation only to definite, so-called *adequate stimuli*. For instance, the cells dispersed over the coverings of earthworms and sensitive to light react only to optic stimuli, while other receptor cells situated close by respond mainly to mechanical stimuli. Special receptor formations located around the mouth are organs responding to chemical stimuli. This differentiation of functions of the receptor apparatuses is connected with a corresponding structure of the nervous system. The cerebral division, which is larger than all the other divisions of the nervous system, becomes particularly important: it gradually develops into the higher centre which can receive impulses from all the receptor apparatuses.

The receptor functions and the nervous system always evolve parallel with the development of the ability to move. The external environment in which the animal exists is a factor which determines its organization. Animals deprived of locomotion receive food from their immediate environment. The number of stimuli in this environment is quite limited, and they act upon the organism through direct contact with the receptor cells (contact receptors). In animals possessing locomotion the anterior end of the body becomes especially important. This part is influenced by the external environment to a greater extent and meets with a greater number of stimuli. As a result, it is here that the most important receptors are situated. Very important changes simultaneously occur in the structure and functions of the receptors. Special receptors are formed to perceive light (electromagnetic) waves, sound waves, chemical stimuli, i.e., receptors by means of which the animal is able to orient itself in distant influences. These receptors are called *distant receptors* (the eye, ear and organ of smell).

The development of distant receptors improves the animal's relationships with the external environment as regards its defensive, alimentary and other reactions. The animal is now able to react to these stimuli even at a certain distance and not only when it comes into direct contact with them.

The further evolution of the receptor systems proceeds in two principal directions, primarily a progressing differentiation of the receptors which reaches the specific development peculiar to man and the higher animals. This improves the function of the analysers, their ability to break up the external environment into very fine, separate, quantitatively and qualitatively different elements. The development of vision in animals, from the most elementary to the highest forms, may serve as an illustration. At first the eye is able to distinguish only between light and darkness; later vision makes it possible to discriminate the forms and details of objects, their distance, colour, etc. At the same time evolution proceeds in another direction, which may be defined as a tendency towards coordination of the special forms of reception with each other and with the motor reactions of the organism. This process, in its most perfect form, is effected by the higher divisions of the central nervous system.

Classification of Receptors

Receptors are structures which respond to stimuli from the external or internal environment of the organism. Normally different groups of receptors are excited by different stimuli. Some receptors are excited by mechanical stimuli; others, by heat or cold. Some receptors are stimulated by chemical agents. Finally, special receptors are excited by sound or light waves.

Thus, the receptors are, as it were, specific detectors of certain stimuli which they transform into nervous processes. They greatly vary morphologically. In some cases they are variously shaped ends of afferent nerves—little hairs, spirals, plexuses, plates, knobs, thickenings, etc. In other cases the nerve ends are connected with specially modified epithelial cells (the receptors of taste and smell). The complex receptor apparatus may be supplied at its periphery with special formations which ensure the access of the external stimuli to the deep-lying nervous receptor elements (the eye, the ear).

All receptors may be divided into two groups, depending on whether they react to changes in the external or internal environment of the organism. These groups are:

a) exteroceptors (external receptors) stimulated by changes in the external environment. They respond to stimuli from external surfaces (visual, acoustic, tactile and thermal receptors), and from the initial divisions of the digestive and respiratory systems (taste and olfactory receptors);

b) interoceptors (internal receptors) located in the blood vessels, the internal organs, the skeletal muscles and tendons. These receptors are stimulated by changes in the activity or state of internal organs and in the pressure or chemism of the blood.

As peripheral apparatuses of the external analysers the exteroceptors are organs perceiving the outer world, while the interoceptors, as the peripheral apparatuses of the internal analysers, have to do with the internal environment of the organism. Both forms of receptors are interconnected through the central nervous system as links of a single receptor system of the organism.

According to the nature of the stimuli which normally excite the receptors, the latter are divided into the following types:

Mechanoreceptors, including the receptors of the skin stimulated by touch, pressure, blows, concussion, etc.; they are also called *tactile* receptors. These include the receptors of the internal organs excited by changes in the pressure on the walls of the organs (*baroreceptors*), or by changes in the tension of the muscles in which they are located.

Chemoreceptors, excited by various chemical substances, are located in the blood vessels, alimentary tract and, possibly, in all tissues; in lower aquatic vertebrates they are also dispersed over the entire skin surface. The skin of mammals has no chemoreceptors reacting to chemical changes in the external environment, since the composition of the atmosphere in which they live does not normally change much; but the mammals have specialized well-developed exteroceptors—organs of taste and smell which are stimulated by chemical agents of the external environment.

Thermoreceptors, responding to temperature changes, are dispersed over the entire surface of the coverings and, possibly, over the entire surface of the respiratory, alimentary and circulatory systems.

Sound and light receptors, represented by the organs of hearing and vision.

A special group is formed by the so-called *pain receptors* excited by stimulations which in some measure injure the coverings of the body or the internal organs. Excitation of these receptors by intense mechanical, chemical and thermal stimulations is subjectively expressed in the sensation of pain.

Relationship Between Intensity of Stimulation and Sensation

Threshold of sensation. The analysers are extremely sensitive to specific, adequate stimuli. The sensitivity of highly differentiated receptors, such as the eye and the ear, exceeds that of the most precise physical instruments. The absolute value of the minimal energy which can evoke the sensation of light is very low. Suffice it to point out, for example, that in clear air a source of light of several thousandths of one candle-power can be seen at a distance of one kilometre. The human ear can perceive oscillations of atmospheric pressure of less than one-thousandth of a bar, which corresponds to approximately one-thousand-millionth of normal atmospheric pressure. And still, everyday experience shows that receptors do not perceive excessively weak stimuli; a stimulus must reach a definite, sometimes very low intensity to produce a sensation.

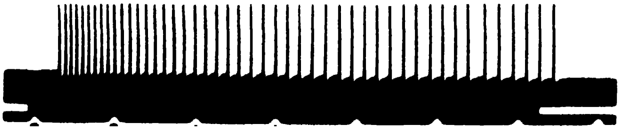

Fig. 285. Gradual diminution of frequency of nervous impulses caused by development of adaptation in receptors. Discharges of nervous impulses have been recorded from one sensory end apparatus (photoreceptor) at constant strength of stimulation. Interruption in white line against black background indicates duration of light stimulus. Time interval—0.2 sec. (after Hartline).

The minimal intensity (quantity) of the stimulus that causes sensation constitutes the *absolute threshold* of sensation. The threshold of sensation is not equivalent to the threshold of stimulation. The absence of sensation during stimulation in no way means that the stimulation exerts no action on the stimulated receptor and produces no physiological effects.

The action of stimuli variously modifies the sensitivity of different analysers. The adjustment of the analysers to the intensity and duration of a stimulus is called *adaptation* (Fig. 285).

The adaptation of analysers manifests itself either in an increase or decrease of sensitivity. With the action of light upon the eye, the sensitivity of vision diminishes, i.e., adaptation to light develops (see Fig. 311); a reverse process occurs in the dark, i.e., the eye adapts itself to darkness. In the latter case the sensitivity of the eye may increase tremendously—by scores and even hundreds of thousands of times. The same phenomenon, though less pronounced, is observed in the adaptation of hearing to silence. The rate at which sensitivity changes during adaptation differs for various receptors. In some receptors, for example, in the tactile receptors, adaptation is quick; in others, for instance, in the pain receptors, and, possibly, in many interoceptors it is insignificant and slow.

Relationship between strength of stimulation and intensity of sensation. When the strength of the adequate stimulus changes, the intensity of excitation which arises in the receptor apparatus and the intensity of sensation change correspondingly. In everyday life we usually appreciate by our sensations the relative rather than the absolute values of the strength of stimuli. It is possible to find a minimal value by which the strength of a stimulus must be changed in order thus to evoke a barely perceptible modification of sensation. This method is used for ascertaining the so-called *differential threshold* of sensation.

Defining the differential threshold of the sensation of pressure, E. Weber (1831) established the following dependence: the value by which the strength of the stimulus must be increased to produce a just perceptible increase of sensation is in a constant ratio to the original value of this stimulus, i.e., always constitutes a definite part of the original value of the stimulus.

In order to obtain a just perceptible increase in the sensation of pressure produced by weight p, it is necessary to increase this weight by a certain value Δp. According to Weber, $\frac{\Delta p}{p} = K$, where K is a constant for the given kind of sensation and does not depend on the original value of the weight. In order to feel the minimal increase in the weight supported by the hand it is necessary, according to Weber, to add to this weight $\frac{1}{17}$ of its value, irrespective of its original value.

This kind of dependence was discovered by the French physicist Bouguer for sensations of light 60 to 70 years before Weber. After Weber's researches it was extended to a number of other sensations, but it proved to hold relatively true only of stimulations of medium strength. To very weak and very strong stimulations the dependence discovered by Bouguer and Weber has proved inapplicable, since fine discrimination in these cases diminishes.

Proceeding from Weber's data and hypothetically assuming (even contrary to actual facts) that continuous intensification of stimulation results in a continuous increase of sensation, the German physicist Fechner expressed the aforesaid dependence by a new formula which is known as "Fechner's fundamental psychophysical law." This "law" is expressed in the following formula: $E = a \ln \frac{I}{Io}$, i.e., intensity of sensation (E) varies directly as the logarithm of the stimulus (I) taken in relation to the threshold (Io). Value a is a constant.

CHAPTER 67

CUTANEOUS RECEPTION

General Characteristics and Kinds of Cutaneous Reception

The surface of the skin is an enormous receptive area and is the peripheral part of the cutaneous analyser. The significance of this analyser is often underestimated, since in the presence of other analysers the role of the receptive function of the skin is largely overshadowed. But in people, deprived, for example, of vision, touch and hearing are the most important kinds of reception.

The following four kinds of cutaneous reception are distinguished: *heat* and *cold* reception which are often covered by the common term of thermal reception; *tactile* reception with its subdivisions, and *pain* reception. A specific stimulus corresponds to each kind of cutaneous reception. Pain sensibility is an exception, since any stimulation of certain strength can evoke pain sensation. Different kinds of cutaneous reception are inherent also in the mucous membranes of the cavities which directly communicate with the external environment. These include the cavities of the mouth, nose, larynx, etc.

In addition to the foregoing principal forms, there are also other kinds of reception which manifest themselves during stimulation of the skin. In most cases they are varieties of separate forms of cutaneous reception or their combinations. For example, there are two varieties of tactile reception: reception of *touch* and reception of *pressure*. A light contact with the skin is perceived as touch sensation; a stronger application of force to the skin, as sensation of pressure. Observations show that the skin is deformed in both cases. Consequently, it is a matter of different intensities of stimulation of the same receptors. Some authors regard the so-called *vibratory sensibility* as a variety of tactile reception, as reception of intermittent pressure. But this point of view is disputed by many clinical physicians-neuropathologists who consider vibratory reception an independent form of reception. The sensation of itch is, probably, one of the peculiar forms of tactile reception.

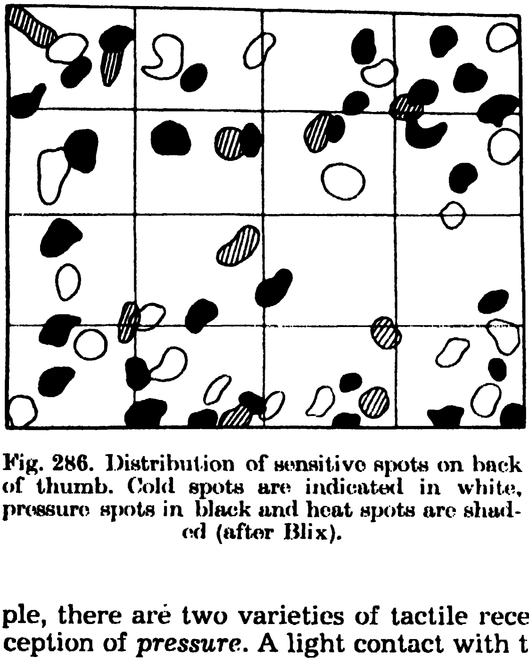

Fig. 286. Distribution of sensitive spots on back of thumb. Cold spots are indicated in white, pressure spots in black and heat spots are shaded (after Blix).

What is usually called the sense of *touch* is an intricate receptor complex resulting from stimulation of receptors belonging to various kinds of cutaneous sensibility.

Different kinds of receptors are unevenly distributed over the skin surface. The number of cold spots in the skin considerably exceeds that of hot spots; there are more pain spots than those reacting to touch or pressure (Fig. 286).

It may be assumed that there is an average of 12 to 13 cold spots and 1 to 2 hot spots per 1 cm.^{2} On the back of the hand there are from 100 to 200 pain spots per 1 cm.^{2} of the skin surface. Most of the tactile spots are located in the skin of the finger-tips, palm of the hand, plantar surface of the foot, tip of the tongue and some other sites. The average number of these spots is about 25 per 1 cm.^{2}

Structure of Cutaneous Analyser

Receptor apparatus of cutaneous analyser. As before stated, the receptor surface of the skin is the peripheral end of the cutaneous analyser, which includes four separate receptor systems producing as a result of stimulation qualitatively different sensations. The structural division of the skin receptors into four categories holds true only relatively. Actually the number of various structures of the nervous end-organs in the skin considerably exceeds that of the aforesaid systems.

Tactile reception is represented in the skin by various receptors (Fig. 287). It is well known that the greater part of the human skin surface (about 95 per cent) is covered with hair, which is sometimes but little developed and therefore hardly perceptible. In the hair-covered skin the tactile receptors are nerve plexuses around the hair bulb. In the hairless skin there are special nerve endings responding to tactile stimulation—Meissner's corpuscles possessing a fine capsule of connective tissue in the deep layers of the skin. Merkel's corpuscles or tactile discs are located in the epithelium of the skin of the hands, legs, breast, back and other parts of the body.

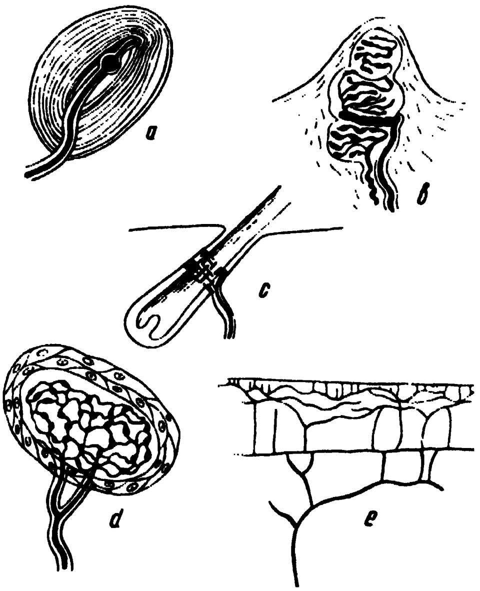

Fig. 287. Receptor end-organs of the skin: *a*—Pacinian corpuscle; *b*—Meissner's corpuscle; *c*—nerve plexus around hair bulb; *d*—Krause's end-bulbs; —free nerve ending.

The end apparatuses of cutaneous thermal reception are not very well known as yet. Krause's end-bulbs are believed to be the specific receptors of cold stimulation; and Golgi-Mazzoni corpuscles, of heat stimulation. Special receptors of pain stimulation are, apparently, represented by the free nerve endings located between the epithelial cells. In the light of the latest experimental data, the existence of special pain receptors seems to be quite probable. However, some authors regard the sensation of pain only as a result of intensified stimulation of the tactile and thermal receptors.

Conducting tracts and brain end of cutaneous analyser. Electrophysiological investigations have shown that all the afferent fibres may be divided into the following three groups according to the rate at which they conduct excitation: group A—myelinated fibres with a diameter of 8 to 12 μ

and with a rate of conduction of up to 120 m. per second; group B—myelinated fibres of 4 to 8 μ and with a rate of conduction of 15 to 40 m. per second; group C—fibres below 4 μ in diameter with a rate of conduction of 0.5 to 15 m. per second. Fine unmyelinated fibres have been found to participate in the conduction of pain impulses.

Within the central nervous system the tracts of the four systems of cutaneous reception are distributed strictly according to their functions.

The nerve fibres connected with tactile and muscular reception run uninterruptedly to the posterior columns of the spinal cord (the columns of Goll and Burdach) and with them reach the medulla oblongata. A secondary tract (*tractus bulbo-thalamicus*), whose fibres cross and proceed to the ventral nuclei of the thalamus, arises in the nuclei of the columns.

The nerve fibres relating to pain and probably thermal reception reach through the posterior roots the gray matter of the posterior horns, whose cells give rise to the second afferent neuron. From here the nerve fibres cross through the anterior commissure to the opposite side, enter the white matter of the lateral columns and form the ***tractus spino-thalamicus lateralis*** whose fibres terminate in the nuclei of the thalamus. From these thalamic neurons axons ascend to the cerebral cortex, but the exact location of the "pain" analyser in the cerebral cortex is still unknown.

The central, or cerebral division of the human cutaneous analyser is formed by the area of the postcentral convolution. Surgical operations under local anaesthesia showed that stimulation of this cortical area by an electric current evoked various tactile and thermal sensations in the patient, though the patient did not feel any pain. But the possibility of elaborating conditioned reflexes reinforced by pain stimulations, which was established in Pavlov's laboratories, testifies to the existence of a cortical representation of pain sensibility.

Experimental unilateral lesions of the brain end of the cutaneous analyser in animals, as a rule, showed derangements in the sensitivity of the skin to touch and to thermal and pain stimulation. These phenomena are transitory; the sensitivity is soon functionally restored, but it is always incomplete. Delicate sensitivity and the ability of precise localization of the site of stimulation disappear for ever. It is quite probable that in a unilateral lesion of the brain end of the cutaneous analyser sensitivity is recovered because cutaneous reception of each side of the body has its own representation in the cortex of both hemispheres. This is also corroborated by the experiments of I. Rosenthal (in Pavlov's laboratory) who demonstrated that in the dog deprived of one cerebral hemisphere a conditioned reflex elaborated to cutaneous mechanical stimulation of the side corresponding to that of the removed hemisphere, is reproduced at once, without preliminary elaboration, when the skin on the opposite side is stimulated.

Tactile Reception

As before stated, tactile reception is characterized by two principal varieties—reception of touch and reception of pressure. Testing the sensitivity of the skin, for example, with Frey's hairs it is possible to establish definite spots which react to pressure, but do not react to thermal stimulation; contrariwise, the receptor end apparatuses which react to thermal stimuli do not react to tactile stimuli. This shows that tactile and thermal sensations are produced by stimulation of different receptors.

A tactile sensation—of touch or pressure—is produced only when the mechanical stimulus deforms the skin surface. Pressure on a very small area of the skin shows maximum deformation directly at the point of application of the stimulus. But pressure on a large surface, for instance by a plate or disc, shows maximum pressure in the parts of the skin lying along the border of the pressed-in area. This can be easily proved by dipping the hand into mercury which has the same temperature as the hand. The sensation of pressure is localized not on the entire surface of the hand submerged into the mercury, but only on the part which passes through the surface of the liquid. If the pressure is evenly distributed over the entire surface of the body, as is the case with atmospheric pressure or hydrostatic pressure during submersion into water, it does not evoke any sensation whatever.

The intensity of sensation depends on the rate of deformation of the skin: the quicker the deformation, the stronger the effect.

Since receptor apparatuses reacting to mechanical stimulations are unevenly distributed over the skin, different areas of the latter possess different sensitivity. In view of this, the degree of sensitivity of each area should be ascertained separately. For this purpose a definite small area of the skin is chosen, and the thresholds of pressure for many of its points are established by means of calibrated Frey's hairs. As a result, a certain mean threshold for the given area is obtained.

If the minimal sensitivity observed in the region of the back, along its mid-line, is taken as one, on the remaining surface of the skin the sensitivity to pressure is distributed as follows.

Abdomen, along the mid-line	1.06
Chest, along the mid-line	1.39
Chest, lateral surface	1.79
Shoulder, flexor surface	3.01
Back of foot	3.38
Area of the radiocarpal joint	3.80
Upper eyelid	7.16
Forehead	7.54

The finger-tips, the tip of the tongue and the border of the lower lip are much more sensitive.

The excitability of the tactile receptors varies with a number of conditions: heating the skin raises the excitability, cooling the skin diminishes it. Mechanical stimulation of the skin rapidly reduces the excitability of the tactile receptors, i.e., they adapt themselves. The duration of the adaptation increases together with the strength of the stimulus, but diminishes with the increase of the stimulated surface.

Localization of mechanical stimulations is very exact. A thorough investigation of the ability to localize tactile stimulations was carried out by Weber who used for this purpose a pair of compasses with blunt points. Weber found that separate sensations were obtained only when there was a definite space between the legs of the compasses. The minimal space required to obtain response to two different stimulations considerably varies in different areas of the skin. The highest sensitivity is exhibited at the tip of the tongue, which responds to two separate stimulations applied 1.1 mm. apart. Then come the volar surface of the fingers, 2.2 mm.; the tip of the nose, 6.8 mm.; the middle of the palm, 8.9 mm.; and finally the mid-line of the neck and of the back, 67 mm.

When pressure is exerted on a large surface of the skin, it is perceived by each end apparatus separately, but the proximity of various receptor points to each other produces a unified sensation.

A conditioned reflex can be elaborated to any mechanical stimulation of the skin (touch, pressure, scratching, etc.). If a tactile stimulus is taken as a conditioned stimulus and a stable conditioned reflex is elaborated to it, all other mechanical stimulations of the skin (pressure, stroking) will evoke a conditioned reaction at their first application without any preliminary elaboration. But tactile stimulations are not fully generalized. Two tactile stimuli situated at different points are easily discriminated. But if the stimuli are situated in symmetric areas of the skin, for example, on the right and left thighs, a differentiation is impossible or it is elaborated with great difficulty and it is unstable.

Thermal Reception

According to widespread ideas, thermal reception includes two separate receptor systems—*heat* and *cold* reception.

Hot and cold receptors are unevenly distributed over the skin surface. A detailed topographic map of heat and cold reception of the skin has been worked out; it has been found that the number of cold spots is considerably larger than that of hot spots. Subsequently a special apparatus, a *thermo-aesthesiometer* consisting of a metallic capsule with a thermometer, was used for studying thermal reception. Water of a certain temperature is passed through the capsule. The latter ends in a cone whose pointed tip is applied to the skin. It has been found that the skin of the trunk is more sensitive to heat than the skin of the extremities; on the extremities the sensitivity of the skin to heat is higher in the distal than in the proximal parts.

The intensity of sensation under thermal stimulation of the skin varies directly with the size of the stimulated area: the same stimulus applied to a larger surface of the skin produces stronger sensation. If a finger is submerged into water having a temperature of 40° C., and the entire other hand into water with a temperature of 37° C., the sensation of heat will be more pronounced in the hand. Strong thermal stimulation evokes a sensation of pain.

The differential threshold, i.e., the threshold of discrimination between intensities of thermal stimulations, depends on the temperature of the area of the body under investigation and on the size of the skin surface subjected to the action of the stimulus. The least discriminable intensity, about 0.5-0.7° C., has been established on the volar surface of the hand under the optimal temperature of the stimulus of 28° C.

The sensation of heat or cold can be evoked by *inadequate stimuli,* i.e., mechanical, chemical or electric stimulation of the thermal points of the skin.

In animals (dogs) and man conditioned reflexes can be elaborated to cold and heat stimulations of various parts of the skin. Thermal conditioned stimuli, especially heat stimuli, possess a peculiar property: inhibition is rapidly elaborated to them, often reaching such intensity that not only the conditioned reflexes disappear, but the dog even falls fast asleep. If a conditioned reflex has been elaborated to heat stimulation of a certain area of the skin, a conditioned reaction can also be obtained without any preliminary elaboration from the entire remaining part of the skin surface by the same stimulus. A reflex to a heat stimulus is widely generalized. If after the formation of a conditioned reflex to a heat stimulus instead of the latter a cold or tactile stimulus is tested, no conditioned reaction arises. This shows that cold, heat and tactile receptions are effected separately.

Pain Reception

Pain sensations are evoked by the action of stimuli which may damage or destroy the tissues of the organism. Pain reception arose in the process of evolutionary development as a form of defensive adaptation to the surrounding medium. The reaction of the animal organism to the influence of external injurious stimuli is aimed at escaping or removing them.

As before stated, pain reception is not connected with the action of stimuli of one definite kind; it emerges under diverse physical and chemical influences. But every pain stimulus has a definite physiological feature—it is injurious.

As to cutaneous pain reception, it is well known from practice that the localization of sensations at the periphery is quite precise. In these cases sensation is always complex since the pain end apparatuses are stimulated simultaneously with the tactile and thermal apparatuses; as regards the latter man is able precisely to localize sensations.

There are about 100 pain spots on 1 cm.^{2} of the skin surface; they are represented by free nerve endings situated in the layers of the skin under the epidermis. Adaptation of the pain receptors is very weak.

Pain stimulation reflexly evokes a number of vegetative reactions which increase the content of adrenalin and sugar in the blood, raise blood pressure and increase blood coagulation (Cannon). Studies of L. Orbeli and his collaborators have shown that intense secretion of hormones of the hypophysis into the blood plays an important role in the reactions to pain stimulations.

Excessively strong pain stimulations may profoundly disturb the regulatory activity of the central nervous system, sharply reduce the blood pressure, weaken cardiac activity, derange respiration and thermoregulation, etc.

Pavlov's laboratories, and subsequently Bykov's co-workers demonstrated that a reaction to pain stimulation could be evoked or suppressed by a conditioned stimulus. These investigations testify to the leading role of the cerebral cortex in the formation of the sense of pain.

Head, a British neuropathologist, proposed that two separate systems of sensibility be distinguished in man: the protopathic (phylogenetically older) system and the epicritic (phylogenetically younger) system. He included pain and coarse thermal sensibility in the first system, and tactile and fine thermal sensibility in the second system. According to Head, both systems are in constant interaction, epicritic sensibility inhibiting protopathic sensibility. Head made this conclusion by observing himself. His observations showed that the cutaneous sensibility after transection of the superficial branch of *n. radialis* recovered as follows: heightened pain sensibility, localized with difficulty, and coarse thermal sensibility appeared first; fine cutaneous sensibility to weak tactile and thermal influences was recovered later. Head's conclusion concerning the separate existence and different phylogenetic periods of the aforesaid types of sensibility is based on the unsubstantiated assumption that the process of recovery of temporarily lost sensibility in man reproduces the phylogenetic sequence of development of different types of sensibility. It will be observed that, according to other authors, who repeated Head's experiment on themselves, the process of recovery of sensibility does not always develop in the sequence observed by Head.

CHAPTER 68

OLFACTION AND TASTE

Olfaction

The receptor apparatuses, whose specific stimuli are different chemical substances, are called chemoreceptors and are the peripheral divisions of corresponding analysers. As before stated, the internal organs and tissues contain a large number of chemoreceptors which belong to the internal analysers. There are two external analysers responding to chemical stimulations; they are the *olfactory* and *taste* analysers. The receptors of the former are usually stimulated by gaseous substances, while the receptors of the latter by solutes. Chemical reception is phylogenetically one of the oldest forms of the organism's connection with the environment.

In aquatic animals the chemoreceptors are stimulated by chemical substances dissolved in the surrounding medium; they function on the principle of *contact* receptors and play a very important biological role. In terrestrial animals the functions of the external chemoreceptors are differentiated: some of them become taste receptors; others, olfactory receptors.

This differentiation is clearly pronounced in insects. Insects possess chemoreceptors which act at a distance and those which act upon direct contact. Of course, these organs can be called olfactory and taste organs only conventionally. In insects olfaction is the most important and most specialized sense after touch, and serves for perceiving odours of different biological significance, such as food odours, the odour of the female, etc.

The olfactory analyser is differently developed in various vertebrates. In some of them the sense of smell is relatively but little developed; these animals belong to so-called microsmatics (birds, monkeys, human beings). Other animals possess a highly developed sense of smell and belong to macrosmatics which include most of the mammals. In some mammals (dolphins) the sense of smell is absent altogether, and they belong to anosmatics.

Structure of olfactory analyser. The pheripheral receptor apparatus of the olfactory analyser is situated in the nasal cavity. In the region of the upper nasal passage and in the posterior upper part of the nasal septum the mucous membrane is thick and of a yellowish brown colour; this is the so-called *olfactory area* which in adults occupies about 2.5 sq. cm. In a newborn child it is considerably larger, the yellowish colour of the mucous membrane overlapping the middle concha.

The receptor apparatus of the olfactory analyser consists of three kinds of cells—*olfactory, sustentacular* and *basal*, which form the *olfactory epithelium.* The olfactory cells are spindle-shaped. The free end of such a cell reaches the surface of the olfactory epithelium and terminates by a swelling—a ciliated *olfactory vesicle.* The olfactory vesicles are immersed in a semiliquid external membrane formed by the sustentacular cells. For every 160 olfactory cells there are about 100 sustentacular cells. The latter, which are of a cylindrical form, pass through the entire thickness of the epithelium and by their bases adjoin the basal cells. The epithelium is also pierced by the ducts of the serous glands. The inner end of each olfactory cell is continued in the shape of a nerve fibre. These fibres come together forming thin threads (*fila olfactoria*), pass through the apertures of the cribriform bone into the cranial cavity and form connections with the nerve cells of the *olfactory bulbs.* Nerve fibres extending from both olfactory bulbs are united into a thick bundle—the *olfactory tract* which on its further way forms a triangular band. The human olfactory tract together with the bulb represents an underdeveloped olfactory gyrus of the macrosmatic animals. From the olfactory triangle the fibres of the olfactory tract extend in separate bundles (Fig. 288); within the lateral olfactory bundle they enter the uncus of *hippocampal gyrus;* a small number of fibres cross through the anterior commissure to the opposite side; some of the fibres extend to the gray matter of *septum pellucidum,* others to *substantia perforata anterior.* In animals with a highly developed sense of smell the latter part of the brain is quite large and is designated as *lobus parolfactorius.*

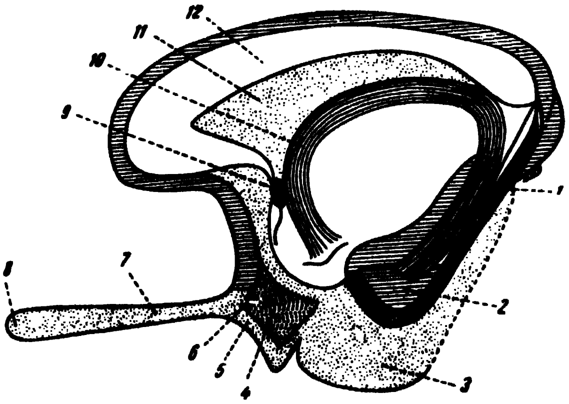

Fig. 288. Olfactory brain (diagram).

1—fascia dentata; *2*—gyr. hippocampi; *3*—uncus; *4*—substantia perforata anterior; *5*—stria latoralis; *6*—stria intermedia; *7*—tractus olfactorius; *8*—bolbus olfactorius; *9*—commissura anterior; *10*—fornix; *11*—septum pellucidum; *12*—corpus callosum.

The cortical division of the olfactory analyser is situated in the region of the uncus of the *hippocampal gyrus,* as was shown at the beginning of this century by Gorshkov and Kastanyan and recently corroborated by electrophysiological studies. The olfactory centres are connected with numerous efferent centres of the diencephalon and midbrain.

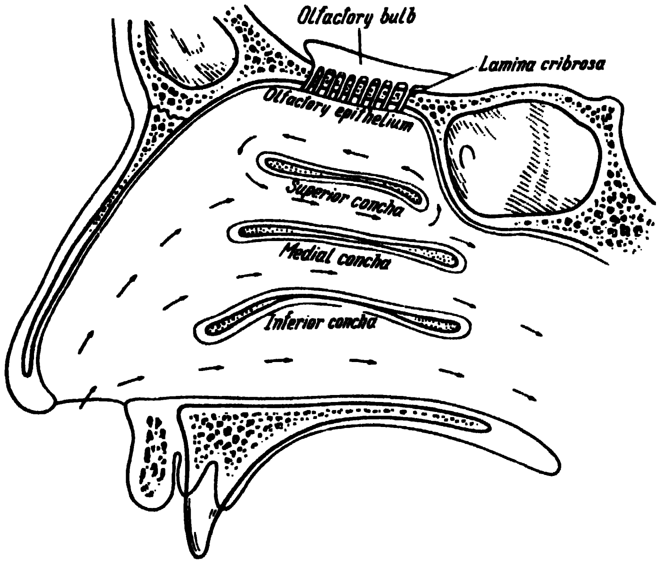

Fig. 289. Right nasal cavity.

show direction of air flow during inspiration.

Mechanism of action of odoriferous substances on receptors of olfactory analyser. Odoriferous substances reach the olfactory area in two ways: when air is inspired through the nose and when it is expired from the oral cavity through the choanae (Fig. 289). During respiration through the mouth, or during quiet respiration through the nose, when the stream of the inspired air almost fully goes through the lower nasal passage, odoriferous substances scarcely reach the mucous membrane of the olfactory area. In order to obtain a distinct sensation of smell, it is necessary to perform one deep inspiratory movement or several quick and short inspiratory movements.

In the act of eating the receptors of the olfactory analyser are stimulated by the air expired through the choanae during mastication. Thus, the olfactory analyser differentiates not only the odour of the air which comes from the exterior through the nasal cavity, but also the odour of food which is in the oral cavity.

Some odoriferous substances stimulate the sensory endings of the trigeminal nerve which lie in the mucous membrane of the nasal cavity. Under the action of these substances, especially in large concentration, reflex changes in the organism, mainly in respiration are observed. Suspension of respiration, often observed at the beginning of ether or chloroform anaesthesia, is an example of such reflex reactions.

It has been found that odoriferous substances such as clove, lavender, anise, benzene, xylene, and many others stimulate only the olfactory cells. These substances belong to purely olfactive (odoriferous) substances. But the odours of camphor, pyridine, phenol, ether, chloroform, etc., which act not only on the olfactory apparatus but also on the sensory endings of the trigeminal nerve, are mixed odours.

Olfactory acuity. The acuity of olfaction is characterized by the threshold of sensation, i.e., the minimal quantity of odoriferous substances which can evoke the sensation of smell. Special apparatuses (olfactometers) for measuring the acuity of olfaction have been designed.

An olfactometer consists of a wide-necked bottle with a capacity of 500 cu. cm., in which a liquid or solid odoriferous substance is placed. Two tubes pass into the bottle through a rubber plug in its neck: one is made of glass, the other of metal. One end of the glass tube, which is bent at right angles, is inserted deep in the bottle; the other end has a rubber head with a cock in it. The exterior end of the short metallic tube is connected through an exhaust valve with a tube which terminates in two olives.

To measure the acuity of olfaction a strictly dosed volume of air is introduced into the bottle with a syringe through the rubber head and glass tube (with cock open); owing to this the pressure inside the bottle (with exhaust valve closed) rises compared with outside pressure. Then the cock is closed and the olives are put into the subject's nostrils. Opening of the exhaust valve with a special lever equalizes the pressure and a stream of air containing vapours of the odoriferous substance, which acts upon the olfactory receptors, enters the nostrils from the bottle.

According to this method, the minimal volume of air (measured in cubic cm.), which must be put into the bottle in order that the stream of air entering the nasal cavity evoke an olfactory sensation, constitutes the index of olfactory acuity, or the "olfactory coefficient." This method makes it possible to introduce strictly dosed amounts of vapours of odoriferous substances into the nasal cavity. The atmospheric pressure and temperature known, it is possible to estimate the partial pressure and the concentration of vapours of odoriferous substances in the bottle.

Table 29 contains data characterizing the acuity of olfaction in man. The concentration of odours is shown in milligrams of odoriferous substance per one litre of air.

Table 29

Odoriferous substances	Intensity of odour		
	Threshold	Weak	Appreciable
Ethylic ether	5.833	10.167	14.944
Chloroform	3.300	6.800	12.733
Ethyl acetate	0.686	1.224	2.219
Pyridine	0.032	0.146	0.301
Butyric acid	0.009	0.021	0.066
Propylmercaptan .	0.006	0.020	0.028
Artificial musk ...	0.00004	—	—

The acuity of olfaction with regard to the same odoriferous substance greatly varies in different people. It also greatly varies with many conditions in the same person. External factors, such as humidity, temperature, atmospheric pressure, etc., considerably affect the variation of the thresholds of olfaction. Internal factors, i.e., changes in the organism, are still more important. For example, the swelling of the nasal mucous membrane resulting from a cold in the head depresses the acuity of olfaction.

Changes in olfactory acuity due to adaptation are particularly pronounced. It is a well-known fact that persons whose work is connected with various unpleasant odoriferous substances soon become so accustomed to these odours that they no longer perceive them. Long-continued inhalation of an odoriferous substance through one half of the nasal cavity results in adaptation not only on the stimulated side, but on the other side as well. It follows that the process of adaptation also occurs in the central divisions of the olfactory analyser. Complete adaptation to a certain odour, i.e., total inability to perceive it, may not affect the acuity of olfaction for other odours.

Taste

The food coming into direct contact with the mucous membrane of the oral cavity is tasted with the help of the taste analyser. The complex mechanism of digestion is reflexly put in operation from the receptive field of the oral cavity.

Structure of taste analyser. The mucous membrane of the oral cavity contains special formations—so-called *taste buds*, which are the specific end apparatuses that respond to taste stimuli. In the adult these taste buds are located predominantly on the tip of the tongue, on its dorsal and lateral surface (except the mid-dorsal region), on the anterior and posterior surfaces of the epiglottis, the back of the pharynx, the anterior uvula and the soft palate. In children the taste buds are scattered over a much wider area than in adults. In old age the number of taste buds diminishes.

Taste buds are found as separate inclusions in the epithelium of the mucous membrane, but on the tongue they are situated around the bases of the papillae. In man there are circumvallate, foliate and fungiform papillae which contain taste buds (Fig. 290).

The taste buds are so located that they penetrate through the entire epidermis, reaching its free surface. They resemble flasks with small openings to the outside—gustatory pores. Each taste bud consists of two types of cells: exterior—sustentacular, and interior—gustatory. Nerve fibres extending from the subepithelial plexus enter the taste buds where they freely terminate; other fibres are situated between individual taste buds.

The innervation of the gustatory area is very complex. Vertebrates do not possess special gustatory nerves as they do olfactory receptors. Taste buds in various parts of the mucous membrane of the oral cavity receive nerve fibres from four different nerves—glossopharyngeal, vagus, facial and trigeminal. The vagus (its branch the superior laryngeal nerve) innervates the larynx, the epiglottis and part of the posterior surface of the tongue; the glossopharyngeal innervates the posterior third of the tongue, while the lingual nerve and the chorda typmani (branch of the facial nerve) innervate the anterior two-thirds of the tongue (Fig. 291). After transection of the gustatory nerve fibres the taste buds degenerate.

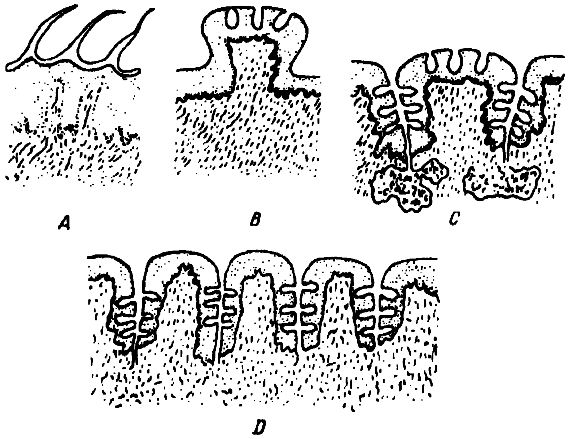

Fig. 290. Taste papillae in tongue.

A—filiform papillae containing no taste buds and related to tactile sensibility; *B*—fungiform papilla; *C*—circumvallate papilla; *D*—foliate papillae.

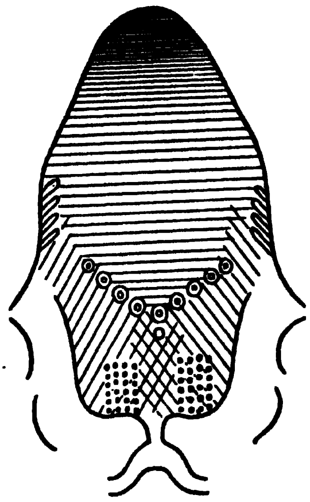

Fig. 291. Innervation of mucosa of tongue.

Horizontal lines—area innervated by lingual nerve; oblique lines—area innervated by glossopharyngeal nerve; dots—area innervated by superior laryngeal nerve.

All the gustatory fibres enter the so-called solitary fascicle (*fasciculus solitarius*) of the medulla oblongata and terminate in the region of its nucleus (*nucleus terminalis*). From here the gustatory fibres (the secondary afferent tract) run to the thalamus where they terminate in the *nucleus ventralis* and *nucleus medialis*. Here is where the third neuron arises. The central, or cortical end of the taste analyser, has not yet been exactly localized. Recent experimental studies, however, have confirmed the old data, according to which the centre of taste is located in the base of the hemispheres near the olfactory area of *gyrus hippocampi*.

Experiments on rabbits localized the taste centre by recording electric potentials which arise in the brain under stimulation of the tongue by various flavouring substances; it turned out that in the region of *gyr. hippocampi*, somewhat posterior to the olfactory area, the electric phenomena were most pronounced. After painting the tongue with a 5 per cent solution of cocaine stimulation by flavouring substances failed to modify the electric potentials.

Flavouring substances and methods of testing taste. The taste receptors are stimulated by most diverse dissolved substances. Substances which are not dissolved in water are tasteless; distilled water is also tasteless. There are four groups of flavouring substances which produce four kinds of primary taste sensations: *sour, salty, bitter* and *sweet*.

Different flavours of our food result from a number of sensations which arise because on the surface of the tongue, along with special taste buds, there are other sensory nerve endings receiving thermal, tactile and pain stimulations. Thus a number of other sensations added by the sense of smell arise simultaneously with taste sensations. A complex combination of stimuli gives rise to different shades of gustatory sensations, such as the metallic taste of colloidal solutions of heavy metals (silver, mercury and others), and the alkaline taste produced by moistening the tongue with a weak solution of caustic alkali or soda.

The *sour sensation* results mainly from stimulation of the gustatory nerve endings by acids or acid salts (by taste alone it is impossible to distinguish hydrochloric acid from sulphuric or nitric acid). If the concentration of H ions is equal, the sensation of sour taste is the same. Very weak solutions of acid do not produce a sour sensation and cannot be distinguished in taste from distilled water. Solutions of mineral acids with a molar concentration of 0.00125 to 0.001 constitute the threshold gustatory stimulus.

Sodium chloride is a typical representative of the group of substances which produce the *sensation of salt*. A similar gustatory sensation is evoked by chlorides of potassium, lithium, ammonia and magnesium. The sensation of salt is due to the presence of anions in the solution. Along with anions of chlorine, the salt taste is conditioned by the presence of anions of iodine and bromine.

The *bitter sensation* is produced by almost all alkaloids and by a number of other substances, such as glucosides, picric acid, ether and some inorganic salts (for example, magnesium sulphate). Alkaloids—quinine, morphine, cocaine, pilocarpine, nicotine, and strychnine—are typical representatives of the group of bitter substances, which possess the highest ability to produce a bitter taste. For example, 0.000005 gr. of strychnine in 5 mls. of solution imparts a distinct bitter taste to the latter.

The group of substances which produce the *sweet sensation* includes diatomic alcohols, or glycols, polyatomic alcohols, monosaccharides (glucose, fructose, galactose, etc.), disaccharides (saccharose, maltose, lactose) and polysaccharides. Thus, various types of sugar possess a sweet taste. but saccharin, and some salts of lead, for example, neutral lead acetate, known as lead sugar, also taste sweet. There are apparently no reasons to assert that a similarity in chemical structure is the only cause of similar gustatory sensations.

In addition to the foregoing adequate stimuli, taste sensations can be produced by stimulating the tongue with electric current. If the anode is applied to the tongue and the cathode to some other part of the body the electric current produces a sensation of sour—a reverse position of the electrodes gives rise to a sensation of an alkaline taste.

Weak solutions of the representatives of the four principal groups of flavouring substances, namely, hydrochloric acid, sodium chloride, quinine and sugar are used to test gustatory sensibility. These solutions are applied to different areas of the tongue with a pipette or a very small sponge attached to a thin stick; fine brushes are used to apply powdery substances.

The tests are performed at intervals of at least five minutes. After each test the mouth is rinsed with distilled water.

Zonal distribution of taste sensibility on surface of tongue. The surface of the tongue is not equally sensitive to various kinds of gustatory stimuli: sweet stimuli are best perceived on the tip of the tongue and least at its base; the basal portion of the tongue is most sensitive to bitter stimuli, while the tip of the tongue reacts least to such stimuli; the tip and edges of the tongue are most sensitive to salt substances, and the middle part of the lateral surface to sour substances.

Thus, the gustatory zones of the tongue differ distinctly in their sensitivity to various flavouring substances, although each area of the tongue containing papillae can simultaneously perceive different gustatory stimuli. This distribution of gustatory sensitivity on the surface of the tongue can be explained if we assume that there are special receptors for each of the four primary taste sensations. Since each papilla contains several taste buds, it can be assumed that some papillae are sensitive to several groups of flavouring substances.

Studies of gustatory adaptation show, for example, that decreased sensitivity to sweet resulting from application of sugar does not affect the sensitivity to bitter, sour or salt substances.

Various taste sensations disappear under the action of different pharmacological substances. When Gymnema acid is applied to the tongue, the sweet and bitter sensations are lost, while the sensitivity to salt and sour stimuli persists. Stovaine acts in a similar way. Cocaine evokes a consecutive disappearance of different kinds of sensibility of the tongue: first pain sensibility disappears, then the bitter, sweet, salt and sour sensations, and, finally, the sense of touch.

It has been demonstrated in K. Bykov's laboratory that the gustatory sensations can be distorted if the conditioned stimulus connected with the action of a substance belonging to one group coincides in time with the action of a substance belonging to another group. In such cases the subject usually perceives the taste of the substance with which the conditioned stimulus is connected.

Experiments with blending various flavouring substances, carried out in P. Lazarev's laboratory, have confirmed the possibility of synthesizing most diverse gustatory properties (the taste of tea, coffee, cocoa, grapes, etc.) with the help of the four principal gustatory stimuli, taken in different concentrations.

Disorders of gustation. The loss of taste sensibility, or ageusia, is observed in various pathological states; it is most frequently a decline of gustatory sensibility, or *hypogeusia*. A case has been described in which all flavouring substances produced only one gustatory sensation, that of salt. There are frequent cases of taste perversion (*parageusia*), when the patients eat various substances loathed by normal people. Diseases of the temporal lobe of the brain may be accompanied by gustatory hallucinations.

CHAPTER 69

INTERNAL ANALYSERS

General Characteristics of Interoceptors

Changes in the internal environment of the organism are perceived by numerous receptors (interoceptors) situated in the walls of the blood vessels and in various organs and tissues. The receptor nerve structures constitute the peripheral division of the *internal analysers* which, like the external analysers, consist of three divisions: the peripheral receptor apparatus, the conductive division and the central end in the cerebral cortex. There is a substantial difference, however, between the functions of the external and internal analysers. Sensations connected with the activity of the internal analysers cannot be exactly localized and are usually diffuse. These sensations include hunger, thirst, urge for urination and defaecation, sexual sensations, etc.; they are of a complex nature and arise as a result of chemical and mechanical stimulations of various receptor apparatuses located in a given system of organs.

Much less is known about the receptor apparatus of the internal organs than about the external receptors. It should be recalled that in the aortic arch and in the region where the carotid arteries divide there are pressure receptors and chemoreceptors. Numerous receptor formations of various kinds—from the Krause bulbs to the pacinian corpuscles and free endings—have been found in the adventitia of the blood vessels, in the gastrointestinal tract and mesentery, in the lungs and other organs. The morphological researches of B. Lavrentyev and of his collaborators have contributed a good deal to the knowledge in this field.

Interoceptors belong to the group of nervous structures whose adaptation is slow and weak. They react to mechanical pressure (mechanoreceptors and baroreceptors), to changes in the chemism of the environment (chemoreceptors), to modifications of the osmotic pressure (osmoreceptors) and to temperature changes (thermoreceptors).

In the laboratories headed by K. Bykov, V. Chernigovsky and other scientists demonstrated the existence of receptors in the pericardium, stomach, intestines, spleen, and other organs. Appreciable electrophysiological material now on hand characterizes the activity of the receptors of the gastrointestinal apparatus. B. Dolgo-Saburov's morphological studies have established the existence of interoceptors in various sections of the venous vascular bed.

All internal receptors are connected with the cerebral cortex, which is proved by the elaboration of conditioned reflexes and differentiations to adequate stimulations of the interoceptors. Such experiments established, contrary to the data of old authors, the existence of thermal sensitivity in some internal organs, particularly, in the stomach. E. Airapetyants elaborated a conditioned reflex to the introduction of water with a temperature of 36° C. into the stomach. When this reflex became stable, he was able to form a differentiation to the introduction of the same amount of water with a temperature of 26° C.

Pavlov's idea of cortical representation of the internal organs was substantiated by electrophysiological experiments which demonstrated the influence of afferent impulses from the internal organs on the bio-electric processes in the cerebral cortex (V. Delov).

Pain Sensitivity of Internal Organs

The internal organs have little or no sensitivity to stimulations whose action on the external surface of the body evokes the sensation of pain. Haller's experiments (eighteenth century) demonstrated that cauterization or sectioning of the organs of the abdominal cavity in animals during feeding did not disturb the act of eating.

Observations on the sensitivity of human internal organs in the course of different operations performed under local anaesthesia prove Haller's findings. As a matter of fact, the mechanical stimulations (sectioning, compressing, suturing, cauterizing, etc.), which a surgical operation inevitably entails, do not evoke any pain sensations when the surgeon deals with the organs of the abdominal and thoracic cavities and with the gray or white matter of the brain and spinal cord. Clinical practice shows, however, that internal organs affected by a pathological process can become a source of very keen pain sensations.

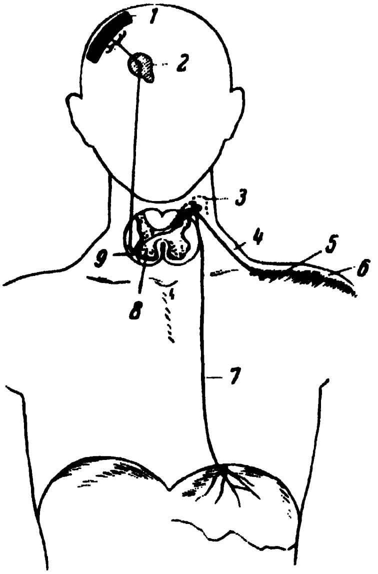

Fig. 292. Diagram illustrating mechanism of referred pain arising during stimulation of diaphragm.

Nervous impulses from diaphragm proceed along phrenic nerve *(7)* through intervertebral ganglion *(3)* to spinal cord *(8)* on level of fourth cervical segment. Here they raise excitability in afferent neuron *(4)* and together with impulses from this neuron pass through internuncial neuron *(9)* to optic thalamus *(2)* and then reach cerebral cortex *(1)*. Pain sensation due to activity of cortex is projected along pathway of neuron *(4)* to periphery, where zone of heightened pain sensitivity *(5, 6)* is created.

All internal organs are supplied with afferent nerve fibres, most of which run in the same trunks as the fibres of the vegetative nervous system (*splanchnic vagus* and other nerves). There is a large number of various receptor apparatuses in the internal organs. Consequently, stimulation influenced by a pathological process may reach the central nervous system and evoke referred action.

G. Zakharyin, and subsequently Head, were the first to discover that diseases of internal organs were very often accompanied by excessive sensibility to pain—hyperalgesia of various areas of the skin (the Zakharyin-Head zones). Heightened sensitivity of the skin is observed in definite metameres (Fig. 238), namely, in metameres receiving afferent fibres from the same segment of the spinal cord that takes in afferent fibres from the diseased organ (Fig. 292). The Zakharyin-Head zones are of great diagnostic significance, since their localization is more or less constant in diseases of the same organ. For example, in heart diseases heightened sensitivity (hyperalgesia) is observed above the left shoulder blade and on the left shoulder. A stomach ulcer is accompanied by hyperalgesia of the skin areas which receive afferent fibres from the sixth and seventh thoracic segments. In visceral diseases hyperalgesia may manifest itself not only on the skin but also in deeper lying tissues—muscles, fasciae, bones. These referred modifications of sensitivity have been named *viscerosensory reflexes.*

Intense *visceromotor reflexes,* for example, a contracture of a definite group of muscles of the abdomen in acute diseases of the abdominal organs (*défense musculaire*), may be observed.

Motor Analyser

The receptor apparatus situated in the muscles, tendons, ligaments and on the surfaces of the joints is of great importance for the fine analysis and precise coordination of movements. The position of the body in space, its postures, and the passive and active movements of separate parts of the body are perceived through this apparatus. Because of this, these receptors are also called organs of muscle-joint sensibility. The receptor apparatus of the muscles and tendons is only the peripheral end of the motor analyser, whose central division is situated in the cerebral cortex.

The central ends of the motor and cutaneous analysers are formed by different cells of the cerebral cortex. This was shown by N. Krasnogorsky in experiments with dogs in which passive flexion of the paw was turned into a signal of an unconditioned alimentary reflex, i.e., into a conditioned alimentary stimulus. Conditioned reflexes to flexion persisted even after removal of the brain end of the cutaneous analyser. But when another part of the cortex—*gyr. sigmoideus*—was removed, a reverse picture was observed: reflexes to flexion disappeared, while stimulation of the skin of the extremity continued to evoke a conditioned reflex.

Contractions and stretching of the muscles and tendons are specific stimuli for the receptors of the motor analyser which are situated in them. This has been convincingly demonstrated by records of action currents which arise in afferent nerves during the contraction or stretching of a muscle.

Not only the stimulations which arise in the muscles during their contraction and in the tendons and joints, but also the stimulations which inevitably occur in the skin at the same time, since each movement is in some measure accompanied by deformation of the skin, are of great importance in the analysis of the position of the body in space and of its displacements.

The role and importance of the motor analyser become particularly clear when the function of this analyser is deranged in one of its divisions, for example, when the posterior roots of the spinal cord are damaged as a result of tabes dorsalis. Considerable disorders of coordination of movements—*ataxia*—are observed in patients suffering from this disease.

The consequences of a lesion of the motor analyser show what an important role the latter plays in the highly complex and varied muscular activity of man. The function of the motor analyser becomes much more precise as a result of the constant participation of other analysers—cutaneous, visual, etc. This participation is so pronounced that in various lesions of the motor analyser its function can be partly replaced by other analysers.

It will be observed that already Sechenov, and subsequently Samoilov, rightfully stressed the important part played by muscular activity (and, consequently, by the motor analyser) in our knowledge of nature and in our ability to influence it.

The great importance of the motor analyser, along with the visual analyser, in such complex acts as perception of space, appreciation of distance, etc., and the role of kinesthetic sensations in speech will be discussed later, in sections of this text-book dealing with vision and speech.

Analyser of Positions and Movements of Head (Vestibular Apparatus)

The special analyser of the position and movements of the head also belongs to the group of internal analysers. The receptor division of this analyser is situated in the labyrinth of the inner ear and is represented by the so-called *vestibular apparatus.*

The vestibular apparatus is often designated as the labyrinth. It should be borne in mind, however, that the labyrinth contains two receptor apparatuses of different physiological significance—the vestibular and the cochlear; the former is connected with the reception of the positions and movements of the head, and the latter with the reception of sounds. It is therefore more correct to use the term "vestibular apparatus" when the analyser of the positions and movements of the body is implied.

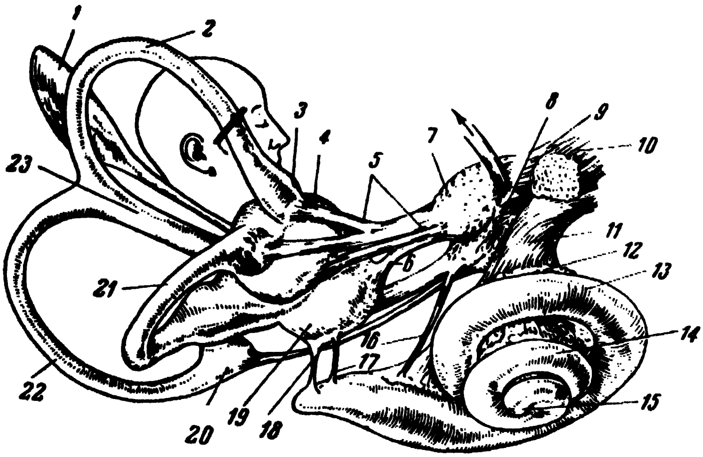

Fig. 293. Diagram illustrating structure of vestibular and cochlear apparatuses.

1—Saccus endolymphaticus; *2*—ductus semicircularis sup.; *3*—ampulla membranacea sup.; *4*—utriculus; *5*—n. utricularis; *6*—n. saccularis sup.; *7* ganglion vestibulare sup.; *8*—ganglion vestibulare inf.; *9*—n. vestibularis; *10*—n. facialis; *11*—n. cochlearis; *12*—ganglion spirale cochleae; *13* and *14*—first ai spirals of cochlear duct; *15*—cupula of cochlear duct; *16*—vestibular end of cochlear duct; *17* ductus reuniens; *19*—sacculus; *20*—ampulla membranacea post.; *21*—ductus semicircularis l ductus semicircularis post.; *23*—crus commune.

Although other analysers—visual, motor and cutaneous—also perceive changes in the position and movements of the head, the vestibular apparatus plays a special role in this respect. It reacts not to uniform rectilinear or rotatory movements, but to acceleration or deceleration of these movements. Persons with an underdeveloped or damaged vestibular apparatus (such persons occur among absolutely deaf people) can distinguish the beginning and end only of jerky movements. Bilateral destruction of the vestibular apparatus in animals gives rise to profound locomotor disturbances; in time, however, these disturbances can be compensated in some measure by the activity of other analysers, mainly, the visual analyser.

The vestibular apparatus includes two little membranous sacs (*utriculus* and *sacculus*) and three semicircular canals (Fig. 293). Each of the sacs filled with endolymph has one elevation or spot (*macula*) which contains the hair cells of sensory epithelium and the endings of the fibres of the vestibular nerve. The free ends of the hairs penetrate the semitransparent gelatinous substance (otolith membrane) which contains microscopic crystals of calcium phosphate and calcium carbonate.

The membranous semicircular canals are situated in the osseous canals of the labyrinth which lie in three planes at right angles to one another—the frontal, sagittal and horizontal planes (Fig. 294). The canals contain endolymph and communicate with the utricle through five openings: the bends of two canals (superior and posterior) are connected. At the end of each canal which opens into the utricle, there is a thickening (*ampulla*) within which lies a small prominence—a *crest* (*crista ampullaris*). The latter is a receptor structure which contains endings of the fibres of the vestibular nerve. It consists of sensitive epithelial hair cells and sustentacular cells. The hairs project into a dome-shaped semitransparent mass (*cupula ampullaris*) which covers the entire length of the crest (Fig. 295).

As before stated, accelerated or decelerated rotation is an adequate stimulus for the semicircular canals. The endolymph contained in the semicircular canals is displaced by inertia and deflects the cupula. This bends the sensitive hairs which stimulates the nerve endings.

Other adequate stimuli of the otoliths are: acceleration or deceleration of rectilinear motion, jolting, tossing, and any changes in the position of the head and of the whole body, which displace the otolith membrane. In these cases they are stimulated by tension of the sensitive hairs or the pressure of the otolith membrane upon them.

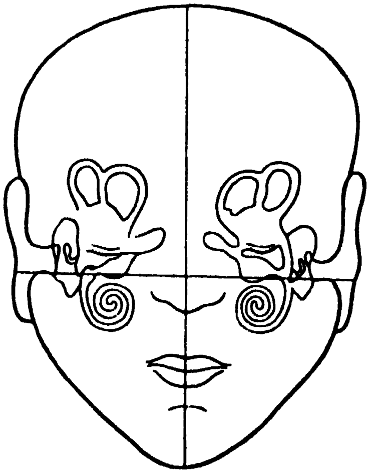

Fig. 294. Location of semicircular canals and cochlea in bones of skull (diagram).

The primary neuron of the vestibular nerve (*ganglion vestibulare*) is situated in the internal auditory meatus. Each cell of this ganglion gives off two processes: one of these processes extends to the otolith apparatus or to the ampullae of the semicircular canals, the other to the medulla oblongata. The central processes form the root of the vestibular nerve. On reaching the medulla oblongata some fibres of the root run to the vermis of the cerebellum and some terminate in the so-called vestibular nuclei lying in the region of the tectum of *pons Varolii*. Part of the root of the vestibular nerve which reaches the nuclei of the medulla oblongata divides into a descending and ascending bundles; the former ends in Deiters' nucleus (*nucleus n. vestibularis lateralis*), the latter in Schwalbe's (*nucleus vestibularis medialis*) and Bekhterev's (*nucleus superior*) nuclei. Fibres issuing from the vestibular nuclei run to the nuclei of the cerebellum, from where they proceed to the higher structures and further to the cerebral cortex. Deiters' nucleus projects a descending bundle of fibres which, apparently, conducts vestibular reflexes to the muscles of the neck, trunk and limbs; it also projects fibres extending to the nuclei of the motor nerves of the eye muscles. These fibres are pathways along which vestibular reflexes to the motor apparatus of the eye (nystagmus and compensatory pose of the eyes) are effected.

The central division of this analyser is situated in the cerebral cortex. Although this division has not been localized yet, clinical and experimental data show a connection between the cerebral cortex and the vestibular apparatus. One such proof is the possibility of elaborating conditioned reflexes to rotation (N. Popov). A special chamber with a dog in it was suspended from a strap, and the unwinding of the latter was used as a conditioned stimulus. Ten to fifteen seconds after the beginning of rotation acid was introduced into the dog's mouth. After several such combinations conditioned salivation appeared as a result of rotation alone. For control purposes a differentiation to rotation in the opposite direction was elaborated.

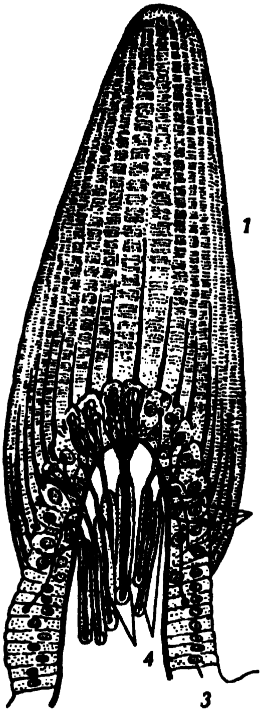

Fig. 295. Structure of receptor apparatus of semicircular canals.

Section through cupula and crista ampullaris *(1)*; *2*—cells with hairs immersed in dome-shaped jelly-like mass covering crest; *3*—sustentacular cells; *4*—endings of nerve fibres surrounding sensory cells (after Kolmer).

The vestibular apparatus not only perceives acceleration of rotational and linear motion, but is also a receptive field for a number of reflexes which evoke appreciable changes in the organism. These changes may be expressed in the redistribution of the muscular tone of the neck, trunk, limbs and eyes (Chapter 58).

The usual method applied in the clinic and in experimental research for adequate stimulation of the semicircular canals consists in rotation on the vertical axis on the so-called chair of Bárány at the rate of one rotation per two seconds. During this rotation the eyes of the subject are closed: depending on the position of the head it is possible to stimulate the three pairs of semicircular canals separately. A number of symptoms developing as a result of such stimulation are used for ascertaining the excitability of the vestibular apparatus.

As a rule, rotation is followed by *postrotatory nystagmus*—quick rhythmic jerking of the eye balls in the direction opposite to rotation. This nystagmus usually lasts 25 to 40 seconds and sometimes up to 80 seconds and over, depending on the excitability of the vestibular apparatus. The duration of postrotatory nystagmus diminishes by training.

Nystagmus can also be evoked by inadequate stimuli: by introduction of warm water (about 43^0 C) into the external auditory meatus or cold water (12 to 30^0 C) (caloric nystagmus), and by passing a galvanic current through the ear (galvanic nystagmus).

Rotation is followed, in addition to nystagmus, by a modification of the muscular tone of the limbs and trunk. In animals this modification is particularly pronounced. In order to detect this modification of the muscular tone in man after rotation, it is necessary to test him for active movements. For this purpose the subject is told to look at an object, then close his eyes and touch it with the hand. The hand usually misses the object (the past-pointing test).

Stimulation of the semicircular canals develops a number of vegetative reflexes: giddiness, sweating, reddening or pallor of the skin, nausea, vomiting, changes in the cardiovascular system, etc. The nature and intensity of such disorders vary in different people. In individuals with a highly excitable vestibular apparatus the nervous system sometimes reacts so violently that a pathological condition (sea and air sickness) results.

The analyser of the positions and movements of the body plays an important role in aviation—in flying a plane. A pilot must have a very sensitive analyser to feel the changes in the position of the plane. It is well known that the threshold of sensation of passive inclinations is considerably higher in the air during flight than on earth (provided the inclinations are equal). On a plane the sensitivity of the vestibular apparatus considerably diminishes due to the influence of vibrations. This is why accelerations developing during flight, when the position of the plane is altered, are not infrequently below the threshold, and the pilot, when unable to make use of his sight, for example, in a fog, cannot fly the plane without instruments.

CHAPTER 70

VISION

General Characteristics of Visual Analyser

The visual analyser is represented at its periphery by a structurally complex nervous formation—the retina, which contains elements sensitive to light—rods and cones. A special light refracting apparatus ensures the focusing of the rays which enter the eye upon the retina. All these structures surrounded by the vascular and supporting coats form the eyeball. The cortical division of the visual analyser is represented by nerve cells in the occipital lobe of the cerebral cortex.

Rays of light constitute the adequate stimulus for the visual analyser. In the spectrum of electromagnetic waves the visible rays occupy only a small region limited by wavelengths of 750 (red rays) to 400 mμ* (violet rays). Recent investigations have shown that the human visual analyser reacts to light rays of a wider range, i.e., 950 to 300 mμ (Pinegin), but sensitivity to the extreme visible rays of this range is millions of times as low.

Full insensibility of the visual receptors to rays with wavelengths beyond the aforesaid limits testifies to the fact that the properties of the eyes have developed in the course of a long evolutionary process aimed at the best possible adaptation to the perception of objects of the external world in sunlight. Biologically the insensibility of the eyes to the long-wave infrared rays is quite comprehensible. It is well known from physics that heated bodies emit light; in slightly heated bodies this luminescence is concentrated in the infrared part of the spectrum. The inner walls of the eye have a temperature of about 37^0 C and also emit infrared rays. Should the photoreceptors of the retina be sensitive to infrared rays, the internal luminescence of the eye would prevent the perception of any external objects. "Compared with this internal light, the sun and the entire surroundings would fade away. A human being would see only the interior of his eye and nothing else, and this would be equivalent to blindness" (S. Vavilov).

The other limit of visibility, in the region of the short waves, is also comprehensible from the biological point of view. This limit is close to the margin of the short-wave section of the sun spectrum. On the surface of the earth the sun spectrum practically ends in the wavelength of about 290 mμ, since shorter waves are stopped in the atmosphere.

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* A millimicron (mμ) equals 0.001 micron or 0.000001 millimetre.

Although Helmholtz, who thoroughly analysed the optic system of the eye, pointed out some imperfections of the eye as an optic apparatus, the visual analyser as a whole is still an extremely sensitive apparatus greatly surpassing all physical instruments. Using the visual analyser as an optic indicator in special experiments Vavilov was able to observe fluctuations of light caused by the uneven flow of quanta of light. Thus the testimony of the eye directly proves the quantum, intermittent nature of light. The maximum sensitivity of the visual analyser varies in different individuals from two to several dozen quanta.

The role of the visual analyser is not confined to mere perception of objects, of their luminosity and colours. Visual sensations are accompanied by afferent impulses from the tendon and muscle receptors of the eye muscles. These impulses arise during the movements of the eyeball and during the activity of the muscles which effect adaptive changes in the apparatus of the eye (changes in the size of the pupil and in the convexity of the crystalline lens). The joint activity of the visual and motor analysers also makes it possible to perceive the shapes of objects, their sizes, movement and distance.

Evolution of Visual Receptor Apparatus

Lower animals perceive light by means of photosensitive cells situated in their external coverings. The concentration of such cells leads to the formation of *optic spots* or *optic foveae*. These simplest eyes consist of a layer of photosensitive cells and of sustentacular cells by which they are supported. In some echinoderms protrusions—optic rods—appear on the surface of the photosensitive cells and a red pigment in the cells. Such photosensitive organs serve for distinguishing the intensity of light and determining the direction of the falling light rays. In addition to the photosensitive cells scattered over the surface of the body worms have structurally complex eyes which resemble the eyes of insects and which, besides retinal elements sensitive to light, also have a primitive optic system in the form of a lens and a cornea.

The compound facet eyes of the Arthropoda (crustaceans, insects, etc.) are of a very peculiar structure: the chitinous covering of the eyes is composed of separate sections—facets. The entire eye consists of many thousands of omatidiums, elongated units arranged at certain angles, and isolated from each other by pigmental layers. Each unit is a rather complex optic system connected with the photosensitive retinal cells. Special experiments on bees and other insects have shown that a facet eye is quite a perfect apparatus with which the Arthropoda can perceive not only the intensity of light, but also the colours and shapes of objects.

Unlike the eyes of invertebrates which develop from the epithelium of the covering (external ectoderm), human eyes and those of vertebrate animals develop from the nervous ectoderm of which the brain, too, is formed. They are outgrowths of the brain.

In the embryo the lateral wall of the anterior cerebral vesicle forms twin protrusions—*primary optic vesicles*. They grow towards the external coverings, at the same time remaining connected with the cavity of the third ventricle through a hollow stem. The anterior wall of the optic vesicle thickens and gradually draws into the vesicle forming a cup or goblet with double walls. As the optic cup comes nearer to the superficial coverings, a thickening is formed in the ectoderm; this thickening submerges into the optic cup, separates and forms the rudiment of the crystalline lens of the eye. The inner layer of the optic cup forms the retina; the external layer, the retinal pigmented layer. The cavity of the optic cup fills with a jelly-like vitreous body. Nerve fibres which grow from the retina towards the brain develop the hollow stem connecting the optic cup with the brain. Thus, on the basis of the nature of the embryonic development of the eye the retina must be regarded as a genuine cerebral tissue, and the optic nerve as the central optic tract.

Phylogenetically the visual analyser in vertebrates evolves in two directions. Owing to the development of the higher divisions of the brain, the higher division of the visual analyser shifts to the cerebral cortex and assumes new functions—those of finest analysis and synthesis. At the same time the development of the eye as an optic system continues: the pupil which does not change in size in fish, is able to modify its size in higher vertebrates due to the development of muscles in the iris; the mechanism which adapts the eye to seeing objects clearly at various distances (accommodation) improves; finally, genuine binocular vision and ability to appreciate distance and relief visually appear.

Structur of Visual Analyser

The peripheral, or receptor division of the visual analyser has a very complex structure. The photosensitive and light-refracting apparatuses are situated in the eyeball.

The wall of the almost spherical eyeball consists of three layers of coats superposed upon one another like the scales of a bulb (Figs. 296 and 297). The coats form the thick capsule of the eyeball which contains a transparent jelly-like substance—the vitreous body.

If we examine an eyeball removed from the eye socket, we shall see on its external surface a fibrous coat called the *sclera*. The anterior portion of this coat forms the transparent *cornea*. In the area of the posterior pole of the eyeball the sclera envelops the trunk of the optic nerve entering the eyeball.

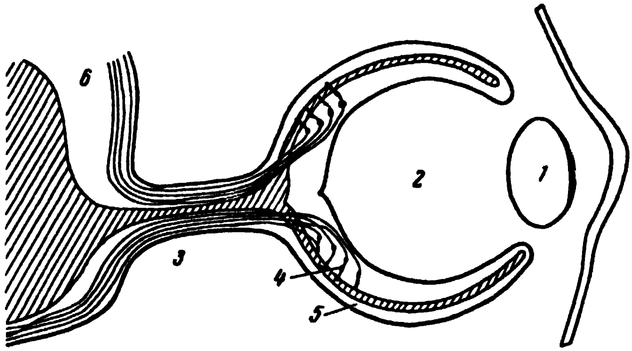


Fig. 296. Diagram illustrating relations of retina and of optic nerve to other parts of brain.
1—lens; 2—eyeball; 3—optic nerve; 4—retina; 5—pigmental layer; 6—cerebral wall (after Herrick).

Under the sclera is the *vascular coat* (chorioidea) abundantly supplied with blood vessels and pigment. Anteriorly, it gradually merges into the *ciliary* body which contains smooth muscular fibres forming the ciliary muscle (*m. ciliaris*). The most anterior portion of the vascular coat is a ring-shaped strip which fringes the pupil and is called the *iris*. The latter is supplied with muscles of two kinds—circular (*m. sphincter pupillae*) and radial (*m. dilatator pupillae*). Contraction of the circular muscles constricts the pupil, while contraction of the radial muscles dilates it. Thus the pupil plays the role of a diaphragm which regulates the intensity of light falling on the photosensitive coat of the eye. The pigmental cells in the iris determine the colour of the eyes. In albinos the iris has no pigment at all.

Behind the iris is a transparent body shaped as a biconvex lens and called the *crystalline lens*. The latter is enclosed in a transparent capsule attached to the ciliary body by the zonule of Zinn. Contraction of the ciliary muscles changes the curvature of the crystalline lens; this is important for the adaptation of the eye to seeing objects at different distances. The space between the cornea and the iris is called the *anterior chamber of the eye*. The small space between the iris and the crystalline lens is known as the *posterior chamber of the eye*. Both chambers are filled with the *aqueous humour*.

The third, innermost coat of the eyeball, or the *retina*, has a complex structure and contains elements sensitive to light, nerve cells and supporting structures. It is about 0.5 mm. thick. The vertical cross-section of the retina of the human eye shows ten layers (Fig. 298); the tenth layer borders on the vitreous body of the eye, while the first layer adjoins the choroid. *Rods* and *cones* are the light-sensitive elements of the eye (Fig. 299). The human eye has a tremendous number of these elements: about seven million cones and several hundred million rods. They are unevenly distributed over the retina. Rods predominate in the peripheral parts of the retina and cones in its central part. Each rod is about 0.07 mm. long; the cones are wider than the rods but shorter. The external limbs of the rods contain *visual purple*, or rhodopsin, which fades under the action of light. The cones contain *iodopsin*, a substance sensitive to light.

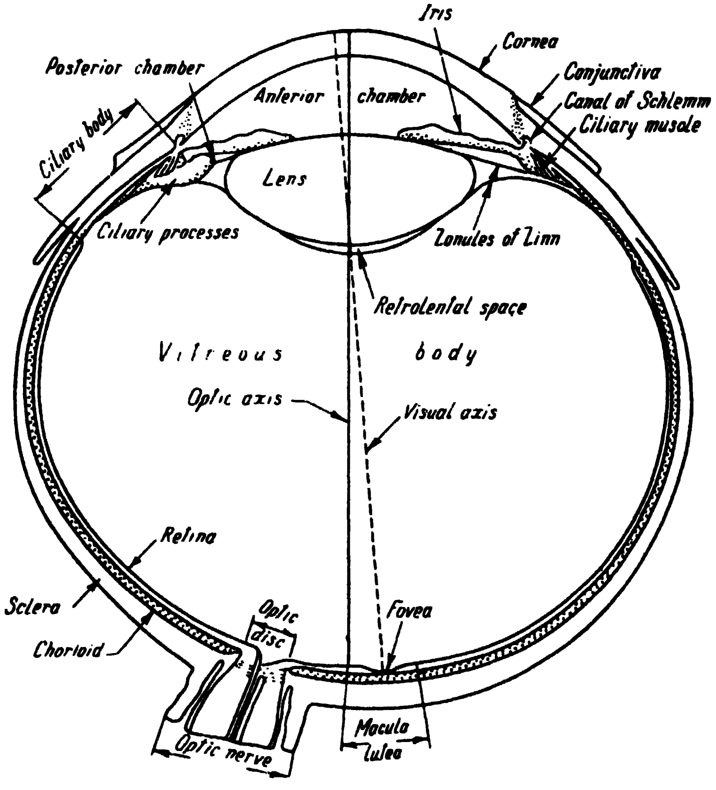


Fig. 297. Schematic horizontal section of right eyeball.

In the posterior part of the retina there are two regions with certain structural peculiarities.

Ophthalmoscopic examination of the fundus oculi at the point where the optic nerve emerges from the eyeball shows the so-called optic disc as a pale spot about 1.8 mm. in diameter (Fig. 301). Since this region of the retina does not contain any elements sensitive to light, it is called the *blind spot*. The existence of the blind spot is demonstrated by Mariotte's experiment (Fig. 302). The blank space in the field of vision, due to the blind spot, is usually not felt, since it is compensated by the activity of the neighbouring regions of the retina.

At a distance of about 4 mm. laterally from the blind spot lies the yellow spot (*macula lutea*), the region of clearest vision. This region, coloured yellow, contains predominantly cones. It is of an elongated oval form, its long axis measuring 2 to 2.9 mm. The central part of the yellow spot is thinned out and has a depression—the *central fovea* which contains only cones.

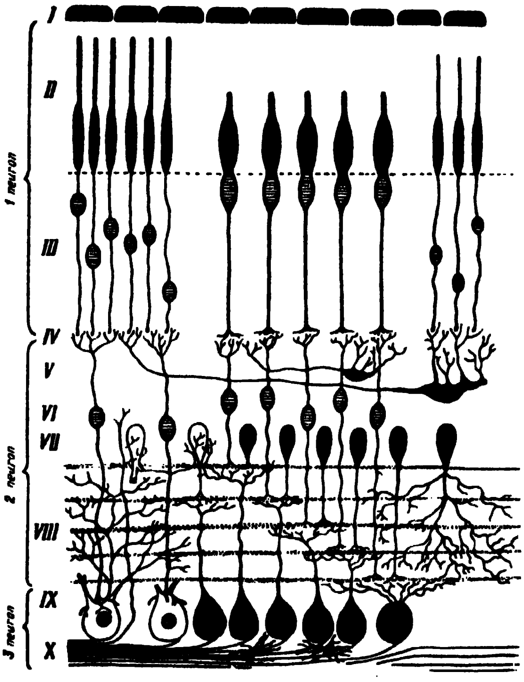


Fig. 298. Diagram of structure of human retina.
I—pigmental layer; *II*—rod and cone layer; *III*—outer nuclear layer; *IV*—external plexiform layer; *V*—layer of horizontal cells; *VI*—layer of bipolar cells (inner nuclear); *VII*—layer of amacrinal (unipolar pyriform) cells; *VIII*—inner plexiform layer; *IX*—ganglion cell layer; *X*—layer of optic nerve fibres. Inner layers imply those which lie closer to vitreous body of eye (after Greeff).

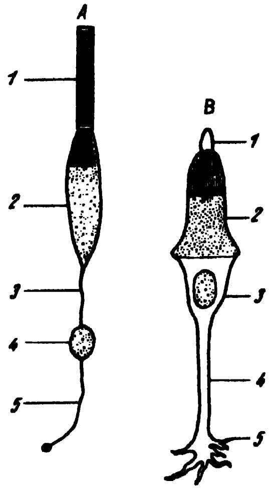


Fig. 299. Rod and cone of retina.
A—rod: *1*—outer limb; *2*—inner limb; *3*—fibre; *4*—nucleus; *5*—end button.
B—cone: *1*—outer limb; *2*—inner limb; *3*—nucleus; *4*—fibre; *5*—stalk.

The rods scattered over the entire surface of the visual part of the retina, except the central fovea, serve for colourless vision, in which all objects seem to be deprived of colour, and which is, therefore, called twilight vision. The cones serve for colour reception. The central fovea, containing almost exclusively cones, is the site of "central vision" particularly sensitive to chromatic rays.

The rod and cone apparatuses of the eye are connected with nerve elements contained in the retina. In the region of the central fovea each cone is connected through an intermediate bipolar cell (Dogiel's corpuscle) with one ganglionic cell in the ninth layer of the retina. In other parts of the retina the number of elements sensitive to light (cones and rods) exceeds the number of bipolar cells, and the number of the latter is greater than that of the ganglionic cells. The farther from the centre of the retina, the more this difference increases.

Thus, one nerve fibre is connected with dozens of end apparatuses. This must favour spatial summation of excitations arising in the photosensitive apparatuses under the action of light.

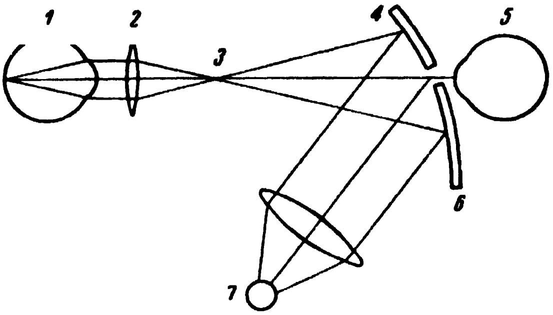


Fig. 300. Diagram of ophthalmoscope.
1—patient's eye; 5—observer's eye; 2—lens of definite focal distance; 4 and 6—concave mirror; 7—source of light with lens.

The conductive division of the visual analyser originates from the ganglionic cells of the ninth retinal layer. The axons of these cells form the so-called *optic nerve* which should be regarded as the *optic tract* rather than a peripheral nerve. On the ventral surface of the brain the optic nerves of the right and left sides cross. In man and apes possessing binocular vision approximately half the nerve fibres of the optic tract decussate (Fig. 303).

After decussation each optic tract contains nerve fibres which extend from the internal (nasal) half of the retina of the opposite eye and from the external (temporal) half of the retina of the eye on the same side. A lesion of the optic tract past the decussation causes a peculiar form of blindness, called half-blindness or *hemianopsia*, since blindness develops in one half of the visual field of each eye. As a result of such unilateral lesion of the optic tract it is the right or left sides of the visual field of both eyes which are affected; this is the so-called *homonymous* form of hemianopsia. The other—*heteronymous*—form of hemianopsia is characterized by the fact that either the medial fields of vision are affected (binasal hemianopsia) or the lateral (bitemporal hemianopsia), which is observed, for example, in lesions of the optic pathways in the region of the decussation (Fig. 303).

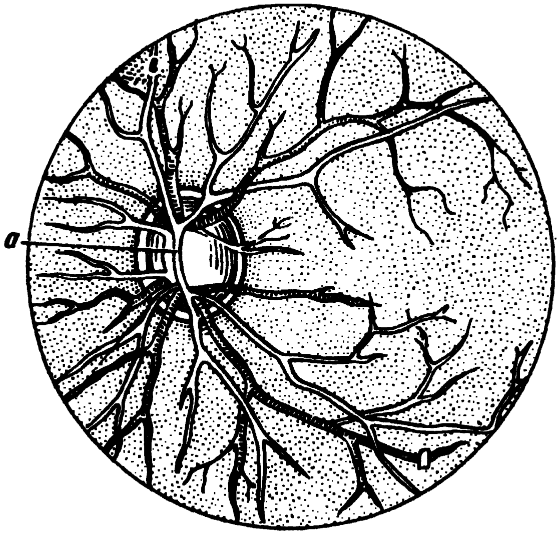


Fig. 301. Ophthalmoscopic view of fundus oculi.
a—optic disc.

The fibres of the optic tract run uninterruptedly to the thalamic region, where they form synaptic connections with the neurons of the thalamus in the *corpus geniculatum laterale*. Some fibres of the optic tract, apparently, terminate in the superior colliculi of the *corpora quadrigemina*. The participation of the latter in visual motor reflexes, for example in the movements of the head and eyes in response to optic stimulations, is indispensable. The lateral geniculate bodies form a relay station which transmits nerve impulses to the cerebral cortex. From here optic neurons of the third order extend directly to the *area striata* of the occipital lobe of the brain.

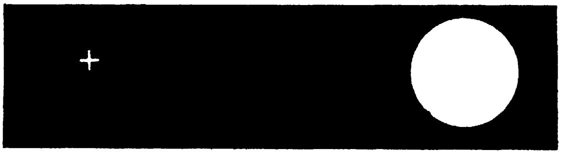


Fig. 302. Mariotte's experiment to demonstrate blind spot of the eye.

Left eye is closed and right eye is fixed on cross marked on card. Card is moved to and from face until at certain distance circle disappears (approximately 25 cm.) because image of circle falls blind spot.

The central division of the visual analyser in man and apes is situated in the posterior part of the occipital lobe—area striata (area XVII, according to Brodmann, see Figs. 278 and 280). It is predominantly the region of the central fovea which is projected here (central vision). Peripheral vision is represented in a more anterior part of the optic lobe.

Experiments with extirpation of the occipital lobe of the brain in various animals show that in lower vertebrates (fish and amphibians) the visual analyser is not represented in the forebrain. Destruction of the occipital lobes in rats impairs the ability to discriminate shapes, but does not affect the ability to differentiate between intensities of light. This ability is also retained in dogs and monkeys after extirpation of the occipital lobes. In man the removal of the optic areas leads to a complete loss of vision (though the reflex constriction of the pupil under the action of bright light persists).

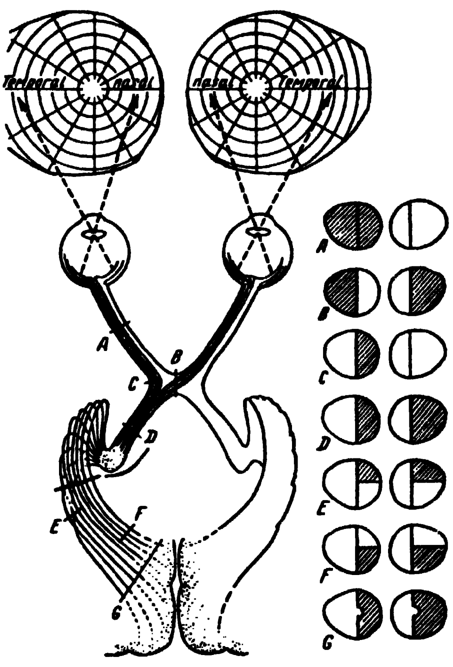


Fig. 303. Diagram of central visual pathways running to left hemisphere.

Left part of figure shows visual pathways; sites of their transection are indicated by letters. Shaded areas in right part of figure indicate under same letters visual fields disappearing after transection. *A*—complete blindness of left eye; *B*—bitemporal hemianopsia; *C*—left nasal hemianopsia; *D*—right homonymous hemianopsia; *E* and *F*—right upper and lower quadrant hemianopsia; *G*—right homonymous hemianopsia with retained central vision (after Homans).

Light-Refracting Apparatus of Eye

Refractive media of eye. In addition to the photosensitive apparatus represented by the retina the peripheral division of the visual analyser contains a complex system of transparent refractive media which makes it possible to obtain on the retina distinct images of visible objects. The presence of such images on the retina can be demonstrated as follows: take an eye of an animal just killed and carefully remove the sclera and the choroid from the posterior wall of the eyeball; place a source of light, for example a lighted candle, before this eye in a darkened room, and you will clearly see an inverted and diminutive image of this candle of the retina.

Rays of light entering the eye pass through a number of refractive surfaces represented by the anterior and posterior surfaces of the cornea, crystalline lens and vitreous body. The path of rays in this optic system is determined by the refractive indices of different media, the radii of the refractive surfaces and some other optic parameters.

The higher the refractive power of the optic system, the shorter the focal distance, i.e., the distance from the optic centre of the system to the point where the refracted rays converge. In ophthalmological practice the refractive power is usually expressed in diopters. One *diopter* (D) corresponds to the refractive power of a lens with a focal distance in air equalling 1 m. If the focal distance of the lens is, say, 0.5 or 2 m., its refractive power is 2 D and 0.5 D respectively.

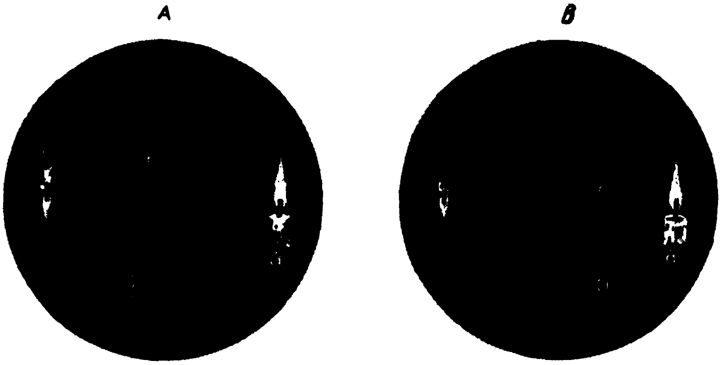


Fig. 304. Modification of Purkinje images during accommodation of eye.
A—before accommodation; *B*— during accommodation for close objects.

The refractive power of the optic media of the eye, expressed in terms of diopters, is 43.05 for the cornea, 19.11 for the crystalline lens at rest and 33.06 in a state of maximum convexity. The refractive power of the entire system of the eye is 58.64, and during maximum accommodation (see below) 70.57.

The usual method of determining the radii of the curvature of refractive surfaces in the eye consists in measuring the size of the images reflected on these surfaces, with the size of the reflected object and its distance from the given surface known. We know from physics that the size of an object is to the size of the reflected image as the distance of the object from the mirror is to the half radius of the latter. This ratio makes it possible to find the value of the radius in question. A special instrument devised by Helmholtz and called *ophthalmometer* is used to determine the sizes of images reflected on the refractive surfaces of the eye.

Accommodation of eye. Clear vision requires that the rays of light from an object produce a distinct image on the retina. Parallel rays of light, i.e., rays coming to the eye from a distant object, are focused on the retina. It may be practically considered that rays of light coming from an object situated at a distance of more than 10 m. from the eye are focused on the retina of the normal eye.

But we can also clearly see near objects, from which pencils of divergent rays fall upon the eye. This is achieved through an increase in the refractive power of the optic system of the eye. The mechanism by which the eye adapts itself to seeing objects distinctly at different distances is called the *accommodation of the eye.*

In man and in all mammals the eye accommodates itself through changes in the refractive ability of the crystalline lens due to modifications of its curvature. Modification of the curvature of the crystalline lens during accommodation is demonstrated by a simple experiment. If a lighted candle is placed before the eye to one side of its axis in a dark room and the eye is observed from the other side at the same angle, three mirror images of the flame will be seen in the eye (Purkinje images, Fig. 304). The brightest of these images (*a*) is reflected from the anterior surface of the cornea and is direct. The second image (*b*), which is also direct, but dimmer than the first, is reflected from the anterior surface of the lens. The third, inverted image (*c*), is reflected from the posterior surface of the lens. If the eye is accommodated for near vision, the second and third images become smaller. The second image (*b*) reflected from the anterior surface of the lens is particularly diminished. It is well known that the image reflected by a convex mirror is the smaller, the smaller the radius of the curvature of the mirror, other things being equal. Consequently, as the eye accommodates itself for near vision the anterior surface of the lens and, to a lesser degree, its posterior surface become more convex.

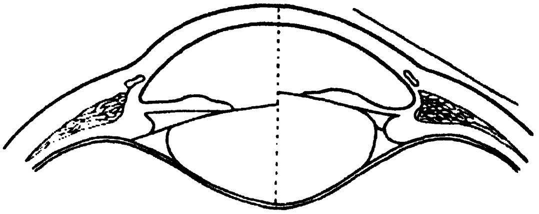


Fig. 305. Modification of lens during accommodation of eye to distant vision (left part of figure) and to near vision (right part) (after Luciani).

A clear idea of the mechanism of accommodation can be obtained from Fig. 305 which shows schematically the state of the lens and of the ciliary muscle during the accommodation of the eye for distant and near vision.

The curvature of the lens during accommodation is modified by a contraction of the ciliary muscle. The contraction pulls the ciliary body forward and thus relaxes the zonules of Zinn which stretch the capsule of the crystalline lens. As a result of the relaxation of the capsule, the elastic lens becomes more convex with the increase mainly in its anterior curvature. The size of the anterior chamber of the eye diminishes.

During full accommodation the radius of the curvature of the lens decreases approximately by 10 to 5.5 mm. on the anterior surface and by 6 to 5.5 mm. on the posterior surface.

The ciliary muscle consisting of smooth muscular fibres is innervated by parasympathetic fibres of the third pair of cranial nerves (oculomotor). Exclusion of the action of the parasympathetic fibres of the oculomotor nerve by introduction of atropine renders accommodation and clear discernment of near-by details (for example, letters) impossible.

Accommodation is always accompanied by a change in the size of the pupil: in looking at a near object the pupil becomes constricted; in looking at a distant object it dilates. During accommodation changes are observed in the direction of the optical axes of the eye; the axes converge.

In normal eyes, convergence and accommodation are directly correlated, and are the more pronounced, the closer the observed object is to the eye.

The limits of accommodation are determined by the near and far points of clear vision. The near point signifies the shortest distance at which the fully accommodated eye can clearly see objects. The far point corresponds to the greatest distance at which distinct images can still be obtained on the retina of the eye with the accommodative muscles in a state of rest. The distance between the near and far points of clear vision characterizes the range or amplitude of accommodation. Within this range accommodation, i.e., the refractive power of the lens, may greatly vary. The amplitude of accommodation can be expressed in diopters; this means that it is possible to determine by how many diopters the refractive power of the eye increases in clear vision of a near point compared with the refractive power in looking at a far point.

Accommodation clearly manifests itself in the fact that the human eye cannot simultaneously and with equal clarity see two objects situated at different distances from it. It is only the observed or fixed object which is seen clearly; all other objects situated closer or farther produce diffused images on the retina and are therefore indistinct. This can be demonstrated by a very simple experiment. If we look through a thin, transparent material (gauze or muslin) at a printed page 25 to 30 cm. from the eye, we shall clearly see the letters, while the threads of the material will disappear from the field of vision; there is a peculiar haze through which the letters can be clearly discerned. But if we fix the eye on the threads of the material, the letters will become blurred.

Measuring the accommodative power of the eye and expressing it in numerical values makes it possible to determine changes in accommodation due to age, and tell the extent of its derangement in pathological cases.

A diminution of the elasticity of the crystalline lens with age leads to the development of old-age hyperopia or presbyopia. Age changes in the accommodation of the human eye are shown in Table 30.

Table 30

Changes in Range of Accommodation With Age

Age in years	Range of accommodation in diopters	Age in years	Range of accommodation in diopters
10	14	45	3.5
15	12	50	2.5
20	10	55	1.75
25	8.5	60	1
30	7	65	0.75
35	5.5	70	0.25
40	4.5	75	0

Refraction of eye and its abnormalities. The refraction of the eye implies its optic properties without any accommodative changes.

If the accommodative muscles of the eye are in a state of rest, i.e., if they are not strained, the focus of its optic system for rays coming from a distant source of light (more than 10 m. away) coincides with the outer layer of the retina. This is the so-called *emmetropic*, or *normal* eye (Fig. 306). If parallel rays falling upon the eye are not focused after their refraction on the retina, but in front of it, the eye is *shortsighted* or *myopic* (Fig. 306). Myopia may be due to excessive refractivity of the eye or to an abnormally long eyeball. In this case all distant objects appear dim and blurred. Glasses with dispersing lenses are used to lengthen the focal distance of rays refracted in the eye.

Shortsighted individuals see near-by objects (for example, letters in reading) distinctly, without accommodation. The accommodative muscles in shortsighted people, therefore, become atrophied.

When the refractive power of the eye is reduced, or the eyeball is shorter than normal, parallel rays are focused after refraction behind the retina. This eye is *longsighted* or *hypermetropic* (Fig. 306). The farsighted person strains his accommodative muscles even to see distant objects owing to which the muscles become hypertrophied. Hypermetropia is corrected by glasses with converging lenses which bring the rays falling upon the eye to a focus on the retina.

Another abnormality in the refraction of the eye is *astigmatism*. It is due to different curvature of the cornea and the crystalline lens along different meridians of the eye. Owing to this, rays falling along one meridian are refracted to a greater degree and cross earlier than other rays refracted along other meridians. In this case no distinct image is obtained on the retina.

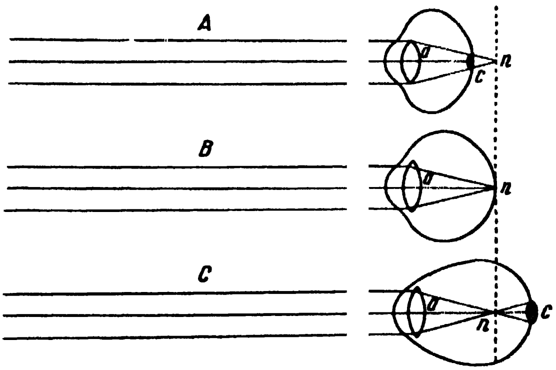


Fig. 306. Path of rays in normal (*B*), farsighted (*A*) and shortsighted (*C*) eye; *n* — focal point of parallel rays falling on eye from distant objects; *a* — optic axis; *c*—circles of light diffraction.

Measurements of the radii of the cornea show that most people have astigmatism, especially along the horizontal and vertical meridians. This physiological astigmatism does not produce any appreciable disturbances of vision as long as it is not pronounced. But beyond certain limits, it becomes pathological and must be corrected by special glasses.

Reaction of pupils. The opening of the pupil has a form of a regular circle with smooth rims. At rest the pupil of the adult has a diameter of 1.5 to 2 mm. in daylight and about 7 mm. in the dark. Changes in pupillary size play the same role as changes in the opening of a camera diaphragm. As before stated, contraction of the ciliary muscle during accommodation is accompanied by a contraction of the sphincter of the iris. When the pupil is constricted, the peripheral rays of the cone of light coming into the eye from the viewed object do not strike the retina owing to which spherical and chromatic aberration diminishes. The pupil limits the optic surface of the cornea and diminishes the astigmatism produced by the irregularities in the cornea's curvature. But the most important physiological function of the pupil is to control the amount of light entering the eye.

The size of the pupil is regulated by the circular and radial muscles. The radial muscle dilating the pupil (*m. dilatator pupillae*) is innervated by sympathetic nerve fibres extending from the superior cervical ganglion. The circular muscle constricting the pupil (*m. sphincter pupillae*) receives fibres from the parasympathetic fibres of the oculomotor nerve. These fibres, like the fibres innervating the accommodative muscle, originate in the Yakubovich-Edinger-Westphal nucleus, which is situated in the tectum of the midbrain. They enter the eye socket in the trunk of the oculomotor nerve and terminate in *gangl. ciliare*. From here the postganglionic fibres penetrate deep into the eyeball and reach *m. sphincter pupillae* and *m. ciliaris.*

The size of the pupil changes under the action of light: a decrease in illumination causes the pupil to dilate, while an increase results in its constriction. This reaction is conjugate, i.e., the pupillary size changes not only in the eye which is under the action of light, but in the other eye as well. The degree to which the pupillary size changes depends on the intensity of light and on the stimulated area of the sensitive surface of the retina; the larger this area, the more the pupil constricts. Other things being equal, the greatest effect is observed when the light falls upon the yellow spot.

The reaction of the pupils to light persists even after the exclusion of the cortical division of the visual analyser, since impulses from the optic tract are switched over to the parasympathetic neurons of the oculomotor nerve in the region of the corpora quadrigemina and the midbrain.

But in the intact organism of higher vertebrates impulses from the cerebral cortex can cause or modify a pupillary reaction like any other function of the organism. This is testified to by reflex changes in the pupils under the action of conditioned stimuli combined with the action of agents which evoke an unconditioned pupillary reflex.

Paralysis of the centres of the oculomotor nerve in asphyxia dilates the pupils to the maximum. This symptom is, incidentally, a very serious warning of impending suffocation in anaesthesia.

Reflex changes in the size of the pupils can also be caused by pain stimulations and by strong excitations of the central nervous system. In these cases the resulting dilation of the pupils is due to the excitation of the sympathetic nerve which produces the contraction of the radial muscle—*m. dilatator pupillae*. In addition, adrenalin and, probably, pituitrin, which act upon the muscular apparatus of the pupil sympathicotropically, enter the blood.

The pharmacological agents which cause the pupil to constrict include: physostigmine, pilocarpine, muscarine, and choline, i.e., substances which produce the same effect as the excitation of the parasympathetic fibres. Atropine and adrenalin, as before stated, produce the opposite effect: they dilate the pupil—the former excludes the action of parasympathetic innervation, the latter stimulates the muscle which dilates the pupil.

Changes in the shape, size and reactivity of the pupil observed in pathological cases are important diagnostic symptoms of certain nervous diseases.

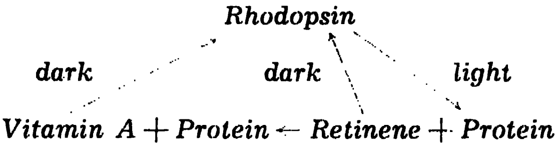
Changes in Visual Analyser Under Action of Light

Photochemical and photomechanical changes in retina. A number of physicochemical and structural changes develop in the retina of the eye under the action of light. The photosensitive substance situated in the external limbs of the retinal rods and called visual purple, or rhodopsin, changes under the action of light. The retina of the eye of the frog or the rabbit, kept in the dark for several hours, is red in its fresh state but almost totally fades when exposed to light for 15 minutes. The visual purple reappears in the dark and its amount reaches the highest level in two hours.

Regeneration of visual purple is closely connected with the existence of a pigmental epithelium which covers the external surface of the retina, and this is where the material for the synthesis of visual purple is, apparently, obtained.

The visual purple fades only in the parts of the retina upon which the rays of light fall. This can be easily demonstrated by the following experiment. The eye of the rabbit kept for some time in the dark is placed opposite an illuminated window. Soon after that the eyeball protected from the action of light is removed from the orbit and subjected to the action of alum. The retina of such an eye shows a so-called *optogram*—in the given case the image of the window in the form of a white rectangle with a purple window-sash. The rate at which visual purple is bleached depends on the wavelengths of the light. Most intense bleaching is caused by the rays which appear to be the brightest in twilight vision (greenish-blue rays). The chemical nature of visual purple remains unknown, but its essential role in the photochemical reactions of the retina is no longer doubted.

On the basis of a number of investigations the picture of chemical transformations in visual purple or rhodopsin can be presented as follows:



Under the action of light rhodopsin dissociates into two molecules: a molecule of retinene (yellow visual substance) and a colourless molecule of protein. It is from these molecules that visual purple is reconstituted in the dark. But if the visual purple has been fully bleached by protracted action of light, it can be synthesized only with the aid of vitamin A. In solutions of pure visual purple, or the yellow visual substance, it is impossible to find vitamin A either by means of photochemical reactions, or spectroscopically. But vitamin A is present in the retina of a dark-adapted eye and is almost absent in the retina of a light-adapted eye. It is possible that vitamin A is supplied to the retina from the food. Vitamin A deficiency leads to a visual disorder called *nyctalopia*, or night blindness, which is characterized by a sharp decline in vision at twilight and at night.

Special experiments on white rats demonstrated the influence of vitamin A on regeneration of the visual purple. Vitamin A deficiency in rats greatly retards regeneration of the visual purple compared with normal.

In addition to the photochemical changes under the action of light the form and position of certain elements of the retina, i.e., the cones, rods and pigment, also change. These so-called retinomotor phenomena are particularly pronounced in certain fish and amphibians, and to a much lesser extent in birds and mammals. The presence of these phenomena in the human retina has not yet been demonstrated. In fish the cones greatly thicken and shorten under the action of light, while the rods stretch in the direction of the pigmental epithelium. At the same time the pigment is displaced inward. In the dark reverse phenomena are observed: the cones and rods change position rather quickly, i.e., in a few minutes; the pigmental particles, however, are displaced slowly. The shape of the cones and rods may change and the pigment be displaced in one eye while the retina of the other eye is subjected to the action of light. The physiological significance of retinomotor phenomena is still unknown. It may be that they create better conditions for the functioning of the retinal receptor elements, in particular, for their protection from the action of excessively strong light.

Bio-electric processes in visual analyser. Changes in differences of the electric potentials which arise in the excitable structures when stimulated by light can be observed in all divisions of the visual analyser—the receptor division (the retina), the conductive division (the optic tract), and the central division (including the cerebral cortex). As before stated, bio-electric changes after their preliminary amplification are recorded by means of an oscillograph.

If one electrode is applied to the cornea of the eye and the other (indifferent electrode) to the mucous membrane of the mouth or the clean-shaven skin of the temple, it is possible to obtain an *electroretinogram,* i.e., to record the changes in the electric potentials which arise in the retina under the action of light.

An electroretinogram (Fig. 307) shows a peculiar curve: its initial phase is characterized by a negative wave (*a*) rapidly followed by a positive wave (*b*); then comes a slow secondary rise of the curve—the positive phase (wave *c*). The cessation of the light stimulation is accompanied by a rise in the curve (wave *d*)—the so-called "off-effect."

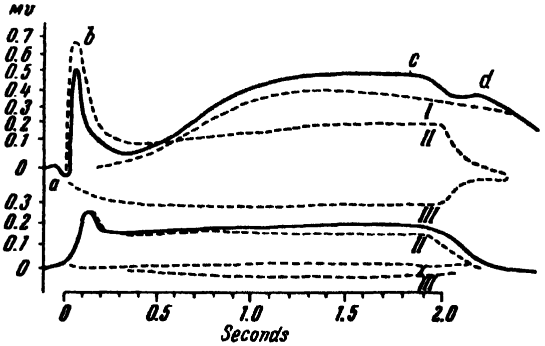


Fig. 307. Analysis of electroretinogram of the cat's eye.

Solid line shows electroretinogram; broken line, its components—*I*, *II* and *III*. Upper electroretinogram was obtained under greater intensity of stimulation than lower one. Bottom—duration of stimulus in seconds; along vertical—values of electric potentials in millivolts (after Granit).

The electroretinogram is simpler when the intensity of stimulation is lower and the stimulated area of the retina is respectively smaller. The latent period, i.e., the period from the beginning of the stimulation to waves *a* or *b*, is in this case longer.

It is possible that the electroretinogram is made up of three curves which constitute its components; they are indicated in Fig. 307 by dotted lines. Component *I* conditions the emergence of the slow positive wave *c*; in etheric anaesthesia it disappears sooner than other components. Component *II* in its initial part forms wave *b*; in deeper etheric anaesthesia it is the second to disappear (after the first component). Negative component *III* is supposed to be associated with the process of inhibition which may arise in the retina under the action of light; it is the most stable component in etheric anaesthesia.

The intricate form of the electroretinogram is probably due to the existence of different types of receptor apparatuses in the retina. There are indications that waves *a* and *b* reflect the activity of the cone and rod apparatus. The slow wave *c* is probably associated with the process of adaptation (see below) which develops under protracted action of the stimulus; however, sufficient experimental proof is still lacking.

The dependence of the length of wave *b* on the accumulation of visual purple in the retina convincingly shows that the elements of the electroretinogram are connected with physiological and photochemical processes in the retina. At the same time the very emergence of wave *b* and its further rise with the accumulation of visual purple occur only when the concentration of visual purple reaches approximately half its maximum value in the course of dark-adaptation.

In the optic nerve it is possible to record action potentials which accompany the passage of afferent impulses. For this purpose the electrodes are applied to two points of the nerve. In a separately taken fibre of the optic nerve the potentials of afferent impulses appear as transient oscillations whose frequency increases with the intensification of the light stimulation (Fig. 308). At the same time the latent period between the beginning of illumination and the emergence of the first impulse diminishes. In response to protracted illumination of the eye the initial frequency of impulses gradually decreases, showing after cessation of stimulation a new, but this time short, outburst of frequent impulses which corresponds to the "off-effect" in the electroretinogram.

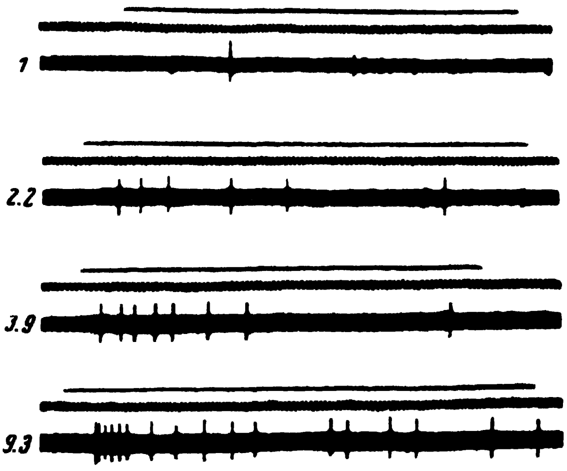


Fig. 308. Electric potentials of afferent impulses in single fibre of optic nerve of guinea-pig under different intensities of stimulation.

Intensity of stimulation by light is indicated in relative units by figures on left side of record (threshold intensity is taken as unit). Duration of stimulus is marked in each case by line above and time interval below (after Granit).

A comparison of electrograms of the retina and of the optic nerve warrants the conclusion that the frequency of impulses in the optic nerve is directly proportional to the degree of intensity of component *II* in the electroretinogram and inversely proportional to the value of inhibitory component *III*.

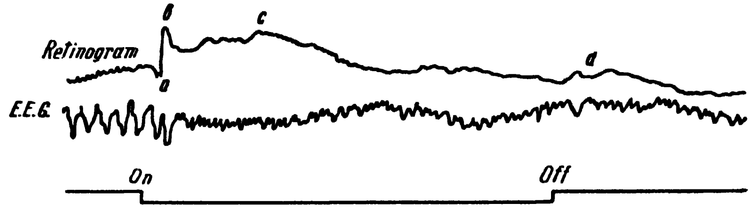


Fig. 309. Simultaneous recording of electroretinogram and electroencephalogram in man (after Spielberg).

The action of a light stimulus on the eye is accompanied by bio-electric changes in the visual area of the cerebral cortex. Changes in an electroencephalogram, recorded with electrodes attached to the skin of the occipital region of the skull, are expressed in the disappearance of the fundamental rhythm—the alpha waves. A simultaneous recording of an electroencephalogram and an electroretinogram is shown in Fig. 309.

If the electrodes are attached not to the scalp, but directly to the visual area (i.e., to *area striata*) of the exposed cerebral cortex, the light stimulation of the eye leads to an outburst of impulses in the form of electric oscillations. When the eye is stimulated by an intermittent, flickering light (Fig. 310, *A*), intense electric oscillations in the visual area of the cortex are observed during the entire period of the stimulation. The frequency of oscillations coincides with the frequency of the flashes, when the latter is low (for example, 4 per second). But when the eye is subjected to a continuous stimulation by light (Fig, 310, *B*), intense electric oscillations are observed in the visual area of the cortex only in the very beginning of the stimulation (the "on-effect") and immediately after cessation of the stimulation (the "off-effect").

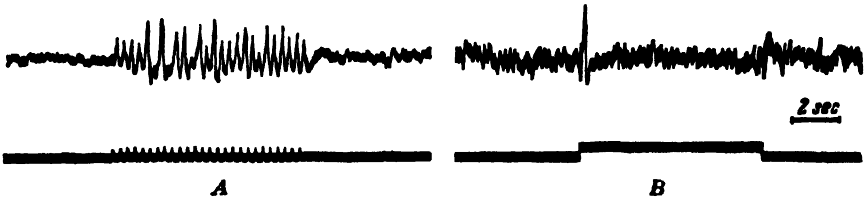


Fig. 310. Bio-electric response of visual area of rabbit's cerebral cortex to stimulation of eye by intermittent *(A)* and continuous *(B)* light.

Upper curves—electrogram; lower curves—marks of stimulation; frequency of flickers in *A*—4 per second (after G. Smirnov).

Light Sensitivity of Visual Analyser

Absolute thresholds of visual sensations. To produce a visual sensation the light rays entering the eye must have sufficient energy and act upon the retina sufficiently long to evoke excitation in the photoreceptors. The minimal amount of light energy required to produce a light sensation determines the absolute sensitivity of the eye. The smaller this amount, the lower the absolute threshold, i.e., the higher the sensitivity of the eye. The threshold value of radiant energy for the eye is extremely low. In sensitivity the eye surpasses any physical instrument. As before stated, the limit of visual sensitivity in man varies, according to S. Vavilov, from two quanta to several dozen quanta. To give a concrete idea of the sensitivity of the visual receptor it should be pointed out that the threshold of optic stimulation is reached by the energy of a visible light falling upon 1 sq. cm. per second from a candle 200 km. away from the eye (assuming, of course, that the atmosphere is absolutely transparent and does not absorb light).

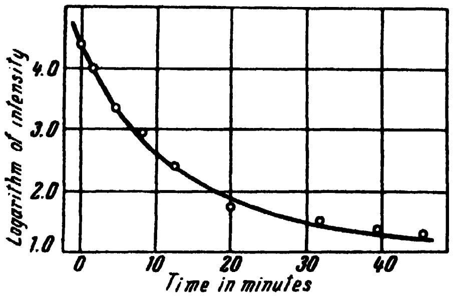


Fig. 311. Curve of dark adaptation of human eye.

Certain conditions must be observed when determining the maximum sensitivity of the eye. To begin with, it depends upon the part of the retina on which the rays of light fall. The spot most sensitive to daylight and colour vision is in the region of the retina where the cone apparatus of the eye is predominantly concentrated, i.e., in the region of the *fovea centralis*; the farther from the fovea centralis and the closer to the periphery of the retina, the lower the sensitivity. As to the so-called twilight, or achromatic (colourless) vision effected by means of the rods, the site of maximum sensitivity is situated to the periphery of the fovea centralis (approximately between 10° and 20° along the horizontal meridian of the retina).

The eye is quite sensitive to changes in the brightness of light. Studies in this field have shown the highest differential sensitivity to be under conditions of moderate brightness.

The differential sensitivity of the eye increases with the increase in its sensitivity during dark-adaptation and with the enlargement of its visual field. At the periphery of the retina differential sensitivity is lower than in the central part. In binocular vision the brightness differential threshold is lower than in monocular vision.

Adaptation. The sensitivity of the eye may vary very widely depending on the intensity of illumination. We know from everyday experience that when we pass from a lighted room into a dark one we see nothing at first, but then gradually adapt ourselves to the darkness. This adaptation of the eye consisting in an increase of its sensitivity is called *dark adaptation*. The reverse phenomenon—*light adaptation*—occurs when the eye is exposed to light after a long period of darkness. At first even relatively faint light seems exceedingly bright and blinding; it takes some time for the ability to see objects distinctly to be restored.

The nature of changes in the intensity of the stimulus threshold during dark-adaptation is shown in Fig. 311. During the first 20 or 30 minutes of darkness the stimulus threshold rapidly declines; then this decline slows down; after a period of 60 to 80 minutes the threshold can be practically regarded as established on a firm level. Strictly speaking, however, the adaptation continues during the entire period of darkness, though it proceeds very slowly.

Not only the rod apparatus of the retina, but also the cone apparatus shows adaptation; the dark adaptation of the fovea centralis is faster than that of the peripheral part of the retina, and takes about 8 or 10 minutes.

According to the photochemical theory of adaption thoroughly elaborated by P. Lazarev, sensitivity of the eye, when it is exposed to light, changes parallel with decomposition of the visual purple. During dark adaptation a reverse process takes place, i.e., regeneration of the visual purple which develops as a monomolecular reaction.

Biochemical and electrophysiological studies show that the process of dark adaptation is effected in the retina. It is not clear as yet, however, whether regeneration of the visual purple underlies the process of adaptation, or merely accompanies it.

The local physiological and photochemical processes in the retina during adaptation by no means exclude the participation of the central nervous system from the phenomena of adaptation. It has been established that in addition to an increase in the sensitivity of the retina during dark adaptation the sensitivity in the visual cortical centres decreases (i.e., the thresholds rise).

A thorough study of dark adaptation has shown that it varies with a number of conditions which develop in the eye itself (for example, various diseases of the eye), and with the influences exerted on the other eye. In experiments performed by S. Krakov stimulation of one eye by white light increased the sensitivity of the other eye; but when one eye was stimulated by red light, the sensitivity of the other eye declined. Yellow light produced a less depressive effect. A modification of the adaptive ability—its decline—was also observed in fasting, in oxygen deficiency, in connection with age, after preceding transient stimulation, etc.

Light adaptation—decrease in the sensitivity of the eye under the action of light stimulation—is, apparently, connected with the expenditure of the retinal photosensitive substance. During light adaptation sensitivity declines rapidly in the first seconds; then it slows down and, finally, reaches a stable level. Light adaptation directly depends on the intensity of light stimulation and its duration. Fig. 308 shows diminution in the frequency of nervous impulses caused in the fibre of the optic nerve by a transient light stimulus of constant intensity during adaptation.

After-images. Excitation arising in the visual analyser under light stimulation does not disappear with the latter, but persists for some time. This is testified to by the so-called after-images which emerge after the stimulus has ceased to act. If we fix our eyes upon a luminous object, for example, upon a lighted electric bulb of sufficient brightness and then close the eyes, we can distinctly see an image corresponding to the initial stimulus. There are two kinds of after-images: *positive*, i.e., fully coinciding with the real stimulus, and *negative*, i.e., representing reverse relations: white becomes dark and vice versa.

After-images are not static; they consist of separate phases rapidly succeeding one another: light phases are succeeded by dark phases, then the light phases appear again, and so on, until the after-image is completely extinguished. The duration of after-images depends on the duration of the stimulation and on the stimulated area of the retina. After-images of faintly illuminated objects are extinguished within one or two seconds, while after strong light stimulations they may persist for several minutes. In some individuals, especially in children, the ability to retain positive after-images is so strong that they can very accurately reproduce visual impressions for a long period after cessation of the stimulation.

The physiological mechanisms of after-images are undoubtedly connected with the aftereffects which persist in the sensitive elements of the retina and which are manifested, in particular, in the "off-effect." A particularly important role in these phenomena is apparently played by the protracted cortical processes with their complex induction relations.

Even very short flashes of light leave an aftereffect in the visual analyser. If the frequency of the flashes is gradually increased, there comes a moment when they fuse, producing the sensation of a continuous, "untwinkling" light. The minimum number of interruptions in light per second at which the flickers become fused is called fusion frequency.

The existence of the aforesaid phenomenon can be demonstrated by a very simple experiment. If a disc divided into white and black sections is rotated fast enough the black and white colours disappear and the surface of the disc becomes uniformly gray. The brightness of the continuous light sensation which arises in this case represents the mean of the sum of luminous effects of all white and all black surfaces (Talbot's law).

Thus, at a high rate of interruptions the sensation becomes as constant as under continuous stimulation, only somewhat weakened. The eye does not perceive any interruptions in the stills of a film demonstrated on a screen at a rate of 24 stills per second, which somewhat exceeds the fusion frequency under conditions of corresponding illumination.

The fusion frequency depends on the intensity of the light stimulus. It may vary with the adaptation of the eye; for example, in peripheral vision, under conditions of dark adaptation the fusion frequency increases.

Colour Vision

Principal characteristics of colour. All colours may be divided into two groups: *achromatic*, i.e., "colourless," and *chromatic*, i.e., having definite colour tones.

All shades of gray, white and black may be included in the *achromatic* group. They differ only in the number of rays reflected, i.e., in brightness. The more rays of light are reflected from a body, the brighter it is. A body fully absorbing all the rays falling upon it would be absolutely black (the surface of black velvet is close to it). All the achromatic colours can be arranged, according to their *brightness*, into a *gray scale*—from pure white through various shades of gray up to and including black. Thus, brightness may be defined as greater or lesser proximity to the white colour.

The eye perceives light waves of different length, or so-called chromatic colours. Usually eight basic colours are distinguished in the spectrum, namely, red, orange, yellow, yellow-green, green, light blue, indigo blue and violet.

The limits of these colours, as expressed by the light wavelengths, are:

Red	760-602 mμ	Green	530-500 mμ
Orange	620-590 mμ	Light blue . . .	500-470 mμ
Yellow	590-560 mμ	Indigo blue . .	470-430 mμ
Yellow-green .	560-530 mμ	Violet	430-390 mμ

By comparing the chromatic colours we can easily see that some of them are bright and others are dark. In a spectrum with evenly distributed energy the yellow-green colours are the brightest, while the red, violet and indigo blue colours are the darkest. But these colours, unlike the achromatic, are distinguished not only by their brightness, but, above all, by their *colouration* or *colour tones.*

Chromatic colours are also characterized by *saturation.* For example, adding white or black to some chromatic colour (red, green, etc.) produces brighter or darker colours of the same tone. The less the colour tone now differs from the gray colour of equal brightness, the lower is its saturation. Thus, it is the degree of difference between a chromatic and an achromatic colour of equal brightness that determines saturation. Various spectral colours differ in saturation: for example, the yellow colours are less saturated than the blue colours.

Changes in colour sensations are usually due to alterations in some of the principal characteristics of the colour. For example, when the colour tone changes, its saturation and brightness also change.

Colour Sensitivity of Visual Analyser

The sensitivity of our eye to different spectral colours varies. The yellow spot whose central part contains only a cone apparatus is the most sensitive; the farther from the yellow spot, the lower the colour sensitivity of the retina. The curve of spectral sensitivity for the average eye in pure cone vision, i.e., when the visual field is greatly limited (at an angle of about 1.5^{0}, according to N. and V. Fyodorovs), shows that the cones are most sensitive to the yellow colour (565 mμ wavelength). Sensitivity diminishes in both directions from this maximum, i.e., towards the red and violet ends of the spectrum.

The curve of spectral sensitivity is also called the visibility curve of spectral radiation. The visibility curve varies with the intensity of illumination. At a low intensity of illumination (for example, in twilight), when the colour tones are no longer perceived, the maximum sensitivity shifts towards the short waves and is then in the region of the bluish-green rays with a wavelength of 500 mμ. This shift of the region of maximum visibility towards the blue part of the spectrum during the transition from day vision to twilight vision is known as the *Purkinje phenomenon.**

As the illumination diminishes, the red colours are the first to become indistinguishable and the blue colours the last. At very high intensities of illumination the colours lose their saturation and turn whitish or yellowish, the violet colour changing most and the red colour least.

The differential sensitivity of the visual analyser to colours varies in different regions of the spectrum. The highest sensitivity is observed in the yellow and light-blue parts of the spectrum; here a difference in the wavelength of 1 mμ is already perceived by the eye. The farther from this optimal regions of differential sensitivity and the closer to the ends of the spectrum, the lower the sensitivity and, finally, the ability to discriminate between colour tones entirely disappears (for example, in the violet part of the spectrum for waves of less than 430 mμ). There are 128 hues generally perceived in the spectrum.

As before stated, the central part of the retina (the yellow spot) which contains only a cone apparatus is the most sensitive to colour. At the same time the peripheral part of the retina which consists mainly of rods is most sensitive to weak light (achromatic) stimuli. It is also known that the retina of the eye of diurnal animals (hens, pigeons, and others) contains only cones, while the retina of nocturnal animals (owls, bats, etc.) contains mainly rods.

It follows that the cones serve for daylight and colour vision, while the rods, specially adapted to low intensities of illumination, serve for twilight, i.e., colourless, vision. The cones characterize central vision, and the rods peripheral vision. This so-called *duplicity theory of the visual apparatus* was recently substantiated by a number of new experiments. For example, L. Orbeli's laboratories have observed definite functional interrelations between both receptor apparatuses of the retina. It appears that a preliminary light stimulation of the region of the yellow spot in the retina retards the increase in sensitivity of the rod apparatus during subsequent dark adaptation. This depressive influence of the centre of the retina on its periphery is later succeeded by an accelerated increase in sensitivity of the peripheral part of the retina.

Colour fusion. For any spectral colour there is another colour, which mixed in suitable proportions with the former will produce white. These pairs of colours are called complementary.

The following spectral colours are complementary: red and bluish-green; orange-yellow and light blue; greenish-yellow and indigo blue; yellow-green and violet. In the spectrum the complementary colours are situated quite far apart. Mixture of colours closer to each other yields intermediary hues lying between the mixed colours.

In this fusion of spectral rays, which is called *optic fusion,* the rays are, as it were, added to each other.

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* Purkinje, a Czech scientist, first discovered this phenomenon in 1823.

Optic fusion of colours should be distinguished from a *mixture of coloured substances,* for example, a mixture of dyes, a fusion of colours resulting from superposition of coloured filters upon one another, etc. In these cases one colour can more or less extinguish another colour; there is a subtraction of colours. The difference between an optic fusion of colours and fusion of dyes is clearly seen from the following fact: fusion of yellow and blue rays produces white; the mixture of yellow and blue dyes, green.

H. Helmholtz

Maxwell's disc is usually employed for the optic fusion of colours. This disc consisting of variously coloured sections is mounted on the axis of a rotating device; when the latter is rotated at the rate of 30 to 40 revolutions per second optic colour fusion is observed. By modifying the size of the coloured sections it is possible to change the quantitative correlations between the mixed colours.

Contrast phenomena consist in an exaggeration of the actual difference between simultaneous and successive sensations. Accordingly, *simultaneous* and *successive contrasts* are distinguished.

Simultaneous contrast manifests itself in both chromatic and achromatic vision. Luminosity contrast is expressed, for example, in the fact that a gray surface placed against a white background appears darker than it really is, while the same gray surface against a black background looks lighter.

In simultaneous colour contrast perception of the colour varies with the colour that surrounds it or borders on it. For example, gray against a red background appears somewhat greenish, while against a blue background it looks yellowish. It may be said that in colour contrast the colour viewed shifts, in some measure, towards the colour which is nearly complementary for the given background.

Successive contrast results from the formation of negative after-images. If the eyes are fixed on a certain coloured figure for 15 or 20 seconds and are then turned on a white surface, the latter will show an image of the same form, but of a different colour.

The physiological mechanisms of contrast phenomena are, apparently, connected with induction relations between the focus of excitation and neighbouring regions in the cortical division of the visual analyser.

Disorders of colour vision manifest themselves both in a lowered ability to perceive colour tones and in partial or total colour blindness.

Total colour blindness is rare. Individuals suffering from this disorder of colour vision distinguish diverse colours of the external environment only by their brightness, i.e., by different shades of gray.

Partial colour blindness occurs more frequently. It is much more frequently observed in men than in women (about 4 per cent of all men suffer from abnormalities of colour vision). Three categories of partial colour blindness are distinguished: protanopia, deuteranopia, and tritanopia.

Protanopia, or *daltonism,* signifies blindness for red and green. Individuals with this defect are unable to distinguish between red and green shades; to them the entire spectrum appears divided by a colourless neutral portion (in the region of rays with a 490 mμ wavelength) into two parts, one having a yellow background and the other a light blue. *Deuteranopia* is also characterized by blindness for red and green, but particularly for green. For the deuteranope the point of maximum brightness is situated in the orange part of the spectrum (600 mμ wavelength), i.e., shifted, as compared with the normal, to the red end of the spectrum. *Tritanopia,* i.e., blindness for blue and violet, occurs very seldom and is characterized by a shortening of the blue-violet end of the visible spectrum.

Individuals with disorders of colour vision are often unaware of this defect. Various colour plates, sets of skeins of coloured worsted or special instruments—anomaloscopes—are used to test colour vision; these tests are very important for preventing people with abnormalities in colour vision from being employed as locomotive engineers, chauffeurs, etc.

Theories of colour vision. Of the numerous theories aimed at explaining colour vision, the so-called *trichromatic theory* seems to be the most substantiated; the fundamental ideas of this theory were first expressed by M. Lomonosov 200 years ago. In his treatise *Discourse on the Origin of Light Presenting a New Theory of Colours* (1756) this brilliant scientist pointed out that "nature is all the more amazing, since ... from a small number of causes it creates countless forms of properties, changes and phenomena." Further he developed the idea that various colours resulted from the fusion of the three primary colours—red, yellow and light blue—and that in accordance with them the "bottom of the eye" contained three colour-sensitive "substances." These basic propositions embody the essence of the trichromatic theory.* But in establishing the three primary colours, Lomonosov proceeded not from colour fusion, but from the results of the mixture of paints.

Only in the beginning of the 19th century was a similar trichromatic theory of colour vision advanced by Young; in the middle of the same century it was thoroughly elaborated by Helmholtz. According to the original supposition of Young, which was close to that of Lomonosov, the primary colours were red, yellow and blue. Later, however, Young correctly defined the primary colours as red, green and blue.

Thus, according to the Lomonosov-Young-Helmholtz theory, the retina of the eye contains three sets of colour-sensitive elements which correspond to the three primary colours—red, green and blue. Each set of these elements is stimulated predominantly by one of the primary colours, but also reacts, though to a lesser extent, to other chromatic rays. The sensitivity curves of the different sets of sensitive elements partially overlap (Fig. 312). The action, say, of red, therefore, stimulates not only the red component, but also, though much less, the green component and very slightly the blue component. Isolated excitation of one set of the sensitive elements evokes the sensation of a saturated colour which corresponds to one of the primary colours. When the three colour-sensitive apparatuses are equally excited a sensation of white results.

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* Lomonosov's aforesaid treatise was published in Russian and Latin. It was also fully presented in the German and English scientific publications of that time.

The trichromatic theory satisfactorily explains the phenomena of colour blindness by the loss of one of the components of colour vision: the red component in protanopia; the green, in deuteranopia; and the blue, in tritanopia.

This theory was recently substantiated by electrophysiological studies (Granit, 1947). Recording the potentials of various points of the retina in cats and frogs with very fine platinum electrodes (microelectrodes) made it possible to determine the thresholds of stimulation (and, consequently, the sensitivity) of various points of the retina on the basis of the arising electric responses. It appears that some retinal receptors possess maximum sensitivity in the region of the red-orange colours, others in the region of the green colour, and still others in the region of the blue colour.

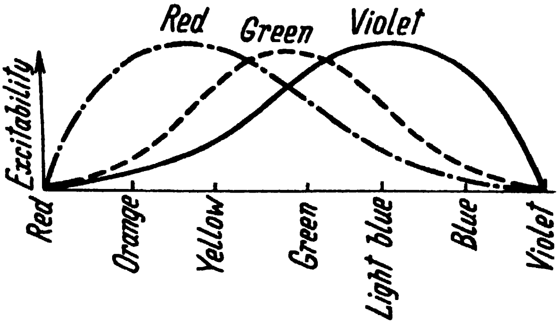

Fig. 312. Diagram of trichromatic theory of colour vision.

Developing the trichromatic theory, P. Lazarev advanced the hypothesis that the photochemical reaction of decomposition of the photosensitive substance is accompanied by a disintregration of molecules and a release of ions, which evoke nervous excitation in the corresponding elements of the retina.

The drawback of the foregoing theory of colour vision is that it reduces the analysis of colour relations, which is effected by the organism, only to the activity of the peripheral division of the visual analyser. It disregards the highly important role of the cortical division in the processes of analysis and synthesis of colour influences. But facts show that colour sensitivity is modified by administration of substances which stimulate or depress the cortex. Many clinical observations reveal cerebral lesions in which colour vision is deranged totally or partly impaired as regards separate colours. Any modern theory of colour vision must therefore consider the highly important role of the cortical factors.

Eye Movements and Spatial Perception

Muscular apparatus of eye. The eyeball moves about the centre of rotation which lies inside the eye 13.5 mm. back of the top of the cornea. It rotates about this centre by means of three pairs of muscles: the lateral and medial erector muscles (*mm. recti lateralis* and *medialis*), the superior and inferior erector muscles (*mm. recti superior* and *inferior*), and the superior and inferior oblique muscles (*mm. obliqui superior* and *inferior*). Each pair of the eye muscles rotates the eyeball on one axis.

In determining the proper directions in which the eyeball will move depending on the contraction of one group of muscles or another, the usual practice is to proceed from a certain primary position of the eyes, which is characterized by the fact that with the head in a straight and vertical position the visual axes are parallel and run sagittally. With the eyes in this primary position the contraction of the lateral or medial recti causes the eyeballs to rotate on the vertical axis. The superior and inferior recti rotate the eyeball on the frontal axis; when the superior rectus is contracted the eyeball moves upward and inward, and when the inferior rectus is contracted it moves downward and inward. The inferior oblique rotates the eye upward and outward, and the superior oblique downward and outward (Fig. 313).

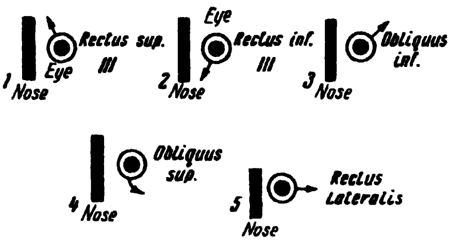

Fig. 313. Diagram illustrating movements of eyeball.

Thus, during vertical movements of the eyeball two muscles are invariably contracted: when the eye moves upward it is the *rectus superior* and *obliquus inferior* muscles, when it moves downward it is the *rectus inferior* and *obliquus superior*. The horizontal movement of the eye is due to the contraction of the medial rectus (inward movement) and the lateral rectus (outward movement) muscles.

The movements of both eyes are normally so coordinated that one eye cannot move without the other.

When the eyes view near objects the visual axes converge due to a contraction of the medial recti muscles. The reverse—divergence of the visual axes—is produced by a contraction of the lateral recti muscles.

The external muscular apparatus of the eye is innervated by three nerves: 1) *n. abducens* innervates the external recti; 2) *n. trochlearis*, the superior oblique muscles; and 3) *n. oculomotorius*, all other muscles of the eye.

As before stated the *n. oculomotorius* also innervates the ciliary muscle of the eye and the muscle which constricts the pupil; owing to this, the movements of the eyeballs are coordinated with certain motor reactions inside the eye, which is of essential importance for clear vision.

As the peripheral end of the motor analyser, the muscular apparatus of the eye plays an important, though not exclusive, part in distinguishing the dimensions of objects. In addition to the size of the image of an object on the retina and to the activity of the external and internal muscles of the eyes, the tactile stimulations which come from it are also very important for furnishing an idea of the dimensions of this object. Pavlov stressed the existence of a conditioned reflex mechanism responsible for the formation of such ideas.

"When, for example, the physiologist is persuaded that to get an idea of the actual dimensions of an object requires a certain size of its image on the retina and certain activity of the external and internal muscles of the eye, he is thereby establishing the mechanism of the conditioned reflex.

A definite combination of stimuli coming from the retina and ocular muscles, repeatedly coinciding with the tactile stimulus arising from an object of a certain size, acts as a signal and becomes a conditioned stimulus produced by the real size of the object. From this point of view, which will hardly be disputed, the principal facts of the psychological part of physiological optics are, physiologically, simply a series of conditioned reflexes, i.e., of elementary facts relating to the complex activity of the eye analyser."*

According to Pavlov, we have in this case what Helmholtz regarded as an "unconscious conclusion" and what is really a conditioned reflex act. The appreciation of distance between objects and the perception of space in general develop similarly, i.e., according to the principle of formation of conditioned reflex connections. Binocular vision is a very important factor in the latter case.

Visual acuity. One of the principal functions of the visual analyser is to determine the spatial relations of visible objects—their dimensions, forms, distance, etc.

The simplest form of spatial vision is discrimination of small objects and details, or so-called *visual acuity.* It is usually measured by the shortest distance between two sources of light which the eye is able to see separately. The higher this ability of discrimination, the greater the visual acuity.

The separate perception of two objects of the external world depends on the size of the image focused on the retina. If the distance between the images on the retina is below a certain limit and if they fall on two adjacent cones, the two objects perceived merge and are impossible to discriminate.

The size of the image on the retina depends on the visual angle.** The smaller the visual angle at which the eye is able to perceive two objects separately, the higher the visual acuity. Therefore, visual acuity can be measured by a value inversely proportional to the visual angle.

It has been established by research that a normal eye can perceive two objects separately if the angle formed by rays proceeding from two separately visible points of an object equals one minute. An angle of one minute is usually regarded by physicians as normal visual acuity. The ability of the eye to see two objects separately depends not only on the distance between the objects, but also on the brightness or luminosity of the visible objects, on the degree of contrast between the objects and the background, on the region of the retina where the image is focused and on the adaptation of the eye. It has been found experimentally that visual acuity is highest with the pupil 3 mm. in diameter. In monochromatic light visual acuity is higher than in mixed light.

Visual acuity is usually measured with special charts, so-called optotypes, containing symbols of different sizes (letters, figures, rings and hooks). Charts which contain letters or rings with breaks and drawn so as to make the width of these breaks or the lines composing the letters visible at angles of 1′, 2′, 5′, 10′ and more, are the most widespread.

In a fixed position the eye perceives a certain space, all points of which are seen simultaneously. This space simultaneously visible by the eye and limited by the insensitivity of the extreme retinal periphery to light stimulations is called the *field of vision.*

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* I. Pavlov, *Complete Works*, Vol. III, Book 1, p. 121.

** An angle formed by rays which proceed from two visible points and cross in the so-called nodal point of the eye, situated at a distance of 7 mm. from the top of the cornea in the direction of the retina.

A special instrument—*the perimeter*—is used for measuring the field of vision. With the arc of the perimeter it is possible to determine the moment when the subject, whose eye is in a fixed position, begins to see the test object (usually, it is a small white spot) slowly moving from the periphery to the centre along the arc of the perimeter. The point on the arc which marks the appearance of the test object corresponds to the outer border of the field of vision along the given meridian. The border is usually determined for four meridians with two points fixed at the opposite ends of each meridian. The data obtained in this way are plotted on respective charts; the outlines of the field of vision of the tested eye are obtained by connecting the points thus found (Fig. 314).

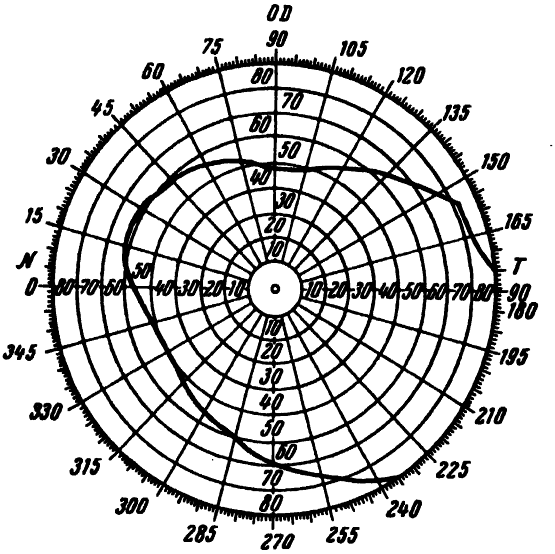

Fig. 314. Normal visual field of right eye for white colour.

The field of vision is the most extensive for the white colour, while for the red, green, yellow and blue colours it is much narrower.

When we look with both eyes, the field of vision of one eye overlaps that of the other eye, owing to which the middle part of the binocular field of vision is common to both eyes.

Binocular vision. We normally see with both eyes, i.e., our vision is binocular. This makes it possible to see the surrounding world in relief, to determine the mutual disposition and distance of objects.

When an object is viewed with both eyes the images focused on the retina of the right and left eyes merge in the cerebral cortex into one image. This merging is possible only when the images of objects fall upon corresponding or identical points of both retinas.

The position of identical points on the retina can be determined as follows. If we imagine the retina of one eye laid over the retina of the other eye so that the central foveae and the vertical meridians of both retinas coincide, the points covering each other will be *identical*. The central foveae of both retinas and all portions of the retinas lying at an equal distance and to the same side from the central foveae should be regarded as identical. The sum of all points of the space the images of which fall on the identical points of the retina are called the *horopter*.

If the image of an object falls in both eyes on retinal points situated at different distances from the central foveae, i.e., the so-called noncorresponding or *disparate* points, double images arise. Such doubling of objects can be observed if, for example, while viewing an object, we displace one eyeball by gently pressing on it with a finger from above or from the side. But if this disparity is not very great no doubling of images is observed;

a new sensation appears—the sensation of some remoteness of the object (perception of depth) compared with the fixed point which produces a single image.

The mechanism of the *stereoscope* is based on this phenomenon. In the stereoscope the relief spatial sensation arises when two plane images of the same object are simultaneously viewed; these images (pictures) are placed before the eyes in such a way that certain parts of them fall on identical points of the retinas and produce a single image, while all other parts fall on retinal points which do not fully correspond to each other and which give rise to an impression of a relief image.

An impression of relief arises not only with a disparity of the images focused on the retina in binocular vision, but also with a convergence of the visual axes. It is possible to judge the distance of objects by the intensity of convergence. Studies have shown, however, that convergence in itself is not indispensable for distance perception, but plays only an auxiliary role.

Visual distance perception is also possible with one eye, though it is not so perfect as in binocular vision. An important role in monocular perception of distance, within the limits of close distances, is played by accommodation which, as is well known, increases as the objects observed are brought closer to the eye.

Differentiation of spatial relations, like perception of the size of objects, is elaborated on the basis of conditioned reflex connections in the activity of the visual and motor analysers owing to the combination of the visual images with the impulses coming to the cerebral cortex from the muscular apparatus of the eyes. Differentiation of the size of objects effected by the cutaneous analyser (tactile sensibility) may play a certain part in this.

Perception of movements. The movements of the surrounding objects are perceived by vision. The perception of movements, which is one of the forms of space perception, may be caused by the displacement of images on the retina. A displacement of images on the retina may be produced by the movement of the object when the eyes are fixed or by the movement of the eyes when the object is motionless.

Perception of movements is possible only when they occur at a certain rate. We do not perceive very slow movements, such as the movements of the hands of a watch; nor do we perceive movements of objects occurring at very high speeds, such as the flight of a bullet. The minimum rate of movement at which the eye is able to perceive the displacement of an object is equal to an angular velocity of 1 to 2′ per second, if the given object moves against the background of motionless objects. The maximum rate at which the perception of movements is still possible depends on the brightness of the stimulus and lies between 1.4 and 3.5 angular degrees per 0.01 second.

Observations show that displacement of the retinal image alone is insufficient for the perception of movements. If, for example, we turn our eyes from one motionless object to other motionless objects we do not perceive any displacement of the intermediate objects. In the perception of movements, as in all other forms of perception of spatial relationships, an important part is played by the movements of the eye, by the activity of the motor analyser connected with these movements and by the conditioned reflex connections elaborated during lifetime.

This is why the studies of various forms of spatial perception based on Pavlov's theory of conditioned reflexes are particularly promising.

CHAPTER 71

AUDITION

General Characteristics of Auditory Analyser

The auditory analyser is a complex nervous mechanism which perceives and differentiates sound stimuli. In the course of evolution the peripheral receptor apparatus of the auditory analyser developed special sensitivity to the action of sound waves whose energy it transforms into nervous excitation transmitted to the central division of the analyser.

The human auditory analyser can perceive sounds ranging in frequency approximately from 20 to 20,000 cycles.* With sound travelling in the air at 340 metres per second this range of frequency corresponds to sound waves of 17 m. to 17 mm.

The sensitivity of the auditory analyser within the range of 2,000 to 4,000 cycles (where this sensitivity is highest) can be characterized by the fact that the amplitude of vibrations of the air particles at the threshold of hearing is about 10^{-10} cm., i.e., much less than the diameter of the air molecules.

From the physical aspect sounds are characterized by frequency (number of periodical vibrations per second) and intensity (amplitude of vibrations). Physiologically the frequency and intensity are correlated with *pitch* and *loudness*. The third important feature of sound is the so-called sound spectrum, i.e., the composition of additional periodical vibrations (overtones) which arise along with the fundamental frequency and exceed it in simple multiple ratios—1 : 2 : 3 : 4, etc. Physiologically this spectrum is expressed in the *timbre of sound*. It is precisely by the timbre that we recognize the sounds of various musical instruments and of human voices even when these sounds are of the same pitch and loudness.

In addition to sounds caused by periodical vibrations and called sound or musical tones, there are diverse sound vibrations of a nonperiodical nature, i.e., noises. Noises and tones may mix together in greatly varying proportions and change into each other, but they are highly delimited in their extreme manifestations.

Very strong sounds evoke a peculiar sensation of pressure in the ear and may even cause pain sensations.

The auditory analyser makes it possible not only to differentiate sound stimuli, but to determine the direction of the sound and the distance of its source (this will be discussed in greater detail below).

Evolution of Auditory Receptor Apparatus

The complex structure and high specialization of the auditory receptor apparatus in man and mammals are the result of long evolution.

Lower animals have special structures called "acoustic tentacles" "acoustic foveae, or vesicles." These structures, previously designated as auditory, are organs of equilibrium. Of the invertebrates only insects possess peculiar auditory apparatuses, so-called tympanic organs, which perceive sound vibrations of a certain range of frequencies.

The auditory apparatus of vertebrates is situated in the membranous labyrinth which is simultaneously the organ of equilibrium. The simplest structure of the labyrinth is in fish. It develops from the ectoderm of the posterior part of the head, first as an acoustic vesicle which communicates with the external surface. Later this vesicle separates and forms three semicircular canals situated in three planes perpendicular to each other. The part of the acoustic vesicle which connects the semicircular canals is called the vestibule (*vestibulum*); it consists of an oval sac (*utriculus*) and a round saccule (*sacculus*). A hollow protuberance (*lagena*) develops in the lower part of the sacculus; in mammals it stretches out and forms the spiral canal of the cochlea.

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* A cycle designates the number of periodical vibrations per second.

The structure of the upper part of the labyrinth is quite uniform in all groups of vertebrates. But the structure of the lower part possesses characteristic distinctions. Already in amphibians and reptiles an extension, called the basilar membrane, becomes separated from the lagena. Inside the protuberance formed by the wall of the sacculus there is a special acoustic papilla (*papilla acustica lagenae*). In birds this protuberance of the hollow saccule becomes elongated and turns into a somewhat curved canal of the cochlea. Inside this canal is situated the main acoustic papilla which is similar in structure to the organ of Corti.

In mammals the auditory receptor apparatus reaches a high level of development. The long protuberance of the sacculus assumes the form of a cochlea with spirals ranging in number from 1½ to 5 in different animals.

This brief outline of the development of the ear labyrinth in animals on different levels of the zoological scale clearly shows that the vestibular apparatus arises earlier than the cochlear. These two portions of the labyrinth are receptors perceiving mechanical vibrations: the vestibular portion perceives coarse concussions resulting from changes in the position of the body in space; the cochlear portion, sound vibrations. The cochlear apparatus begins to develop only when the animals pass to a terrestrial mode of life. The beginning of cochlear formation coincides with the beginning of the development of the cerebral cortex.

As before stated, fishes do not have cochleae; it would, therefore, seem that they have no sense of hearing. But numerous experiments (Frolov and others) have shown that fishes react to sound stimuli providing the lower part of the labyrinth (*sacculus* and *lagena)* is intact. The fact that amphibians and reptiles have a sense of hearing is also beyond doubt. Frogs react to sound stimuli ranging in frequency from 50 to 15,000 cycles, but can hardly distinguish separate sounds. Experiments with elaboration of conditioned reflexes in lizards show that the latter can perceive sounds whose upper limit of frequency is about 8,000 cycles. The sense of hearing is relatively well developed in birds, its upper limit being about 10,000 cycles.

The sense of hearing is developed most in mammals owing to the higher development of the peripheral receptor apparatus and the functions of the cerebral cortex where the higher division of the auditory analyser is located.

Structure of Auditory Analyser

Peripheral division of auditory analyser. The peripheral division of the auditory analyser includes: 1) a sound-collecting apparatus—the external ear; 2) a sound-transmitting apparatus—the middle ear; 3) a sound-receiving apparatus—the inner ear (the cochlea with the organ of Corti). The structure of the peripheral division of the auditory analyser is described in detail in courses of anatomy and histology. Here we shall recall only the structure of the cochlea and of the organ of Corti.

The *cochlea,* with the organ of Corti enclosed in it, is the peripheral receptor apparatus of the auditory analyser which transforms the energy of sound waves into energy of nervous excitation. It is an osseous canal coiled spirally around a conic bony pillar (*modiolus*); branches of the *cochlear* nerve pass through openings in the base of the modiolus. The canal which is 20 to 30 mm. long in man forms $2\frac{1}{2}$ or $2\frac{3}{4}$ spirals and gradually diminishes in diameter from the base of the cochlea to its apex. A spiral osseous lamina (*lamina spiralis ossea*) extends from the axial pillar along the entire canal, its width being about $\frac{2}{3}$ that of the canal. Between the free edge of the spiral lamina and the lateral wall of the canal stretches a thin membrane—the basilar membrane (*membrana basilaris*). This osseous-connective tissue partition divides the canal into two chambers or staircases.

The upper staircase, *scala vestibuli*, communicates with the vestibule and extends to the apex of the cochlea, while the lower staircase, *scala tympani*, extending from the apex, terminates by the round window. At the apex of the cochlea both staircases communicate through a small opening (*helicotrema*).

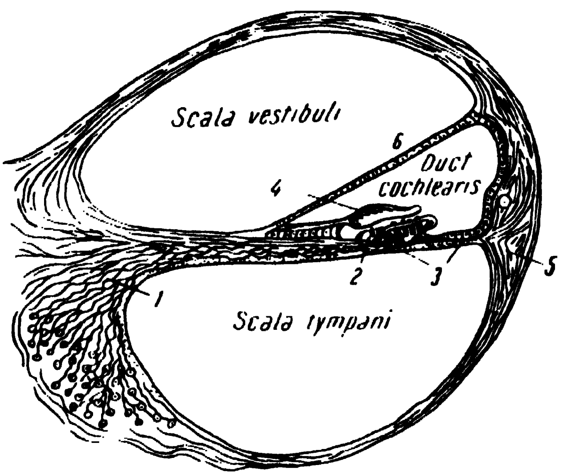

Fig. 315. Cross-section of cochlear spiral (diagram).
1—fibre of cochlear nerve; *2*—organ of Corti; *3*—basilar membrane; *4*—tectorial membrane; *5*—spiral ligament; *6*—Reissner's membrane.

If we make a cross-section of one of the cochlear spirals the preparation thus obtained will allow us to see the inner structure of the staircase (Fig. 315).

The upper staircase is divided by a thin membrane, called Reissner's membrane, into two unequal cavities. The smaller cavity is called *ductus cochlearis* or *scala media*. It extends along the entire canal of the cochlea up to its apex where it terminates in a blind sac. Inside the scala media is the most important part of the cochlea—*the organ of Corti* which is situated along the entire length of the cochlea, on the upper surface of the basilar membrane, along its medial edge. The basilar membrane consists of very fine elastic fibres stretched between the free edge of the spiral lamina and the lateral wall of the osseus canal of the cochlea. The blood vessels are situated on the lower surface of the basilar membrane.

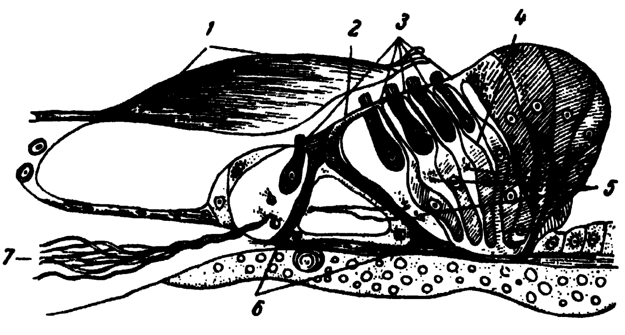

Fig. 316. Diagram of human organ of Corti (cross-section).
1—tectorial membrane; *2*—retiform membrane; *3*—outer (3 to 4 rows) hair cells and inner (one row) hair cells; *4*—sustentacular cells; *5*—fibres of cochlear nerve (cross-section); *6*—outer and inner pillars; *7*—cochlear nerve.

The organ of Corti is a highly complex epithelial formation containing sustentacular and sensory cells. Its structure is shown in Fig. 316.

In the middle of the organ of Corti there is a triangular space called the tunnel. This tunnel extending throughout the length of the cochlea is formed by obliquely mounted sustentacular cells—by the *outer* and *inner pillars* whose upper ends come together forming the arch of Corti.

Medially from the arches of Corti there is one row of acoustic hair cells—the *inner acoustic cells*—and laterally—three or four rows of *outer acoustic hair cells* and *sustentacular cells.* The fibres of the auditory nerve form a very fine plexus around the acoustic hair cells, which are the sensory cells of the auditory organ. The hairs of the acoustic cells enter the lumen of the scala media which is filled with endolymph. There are about 3,500 inner hair cells and about 20,000 outer hair cells.

Projecting over the organ of Corti is the *membrana tectoria.* One of its ends is attached to the edge of the osseous spiral lamina and the other is freely immersed in the endolymph.

While the diameter of the osseous canal gradually diminishes in the direction of the cochlear apex, the width of the basilar membrane changes in the opposite direction: its narrowest part is at the base of the cochlea, near the round window and the vestibule; its broadest part is in the region of the upper spiral of the cochlea.

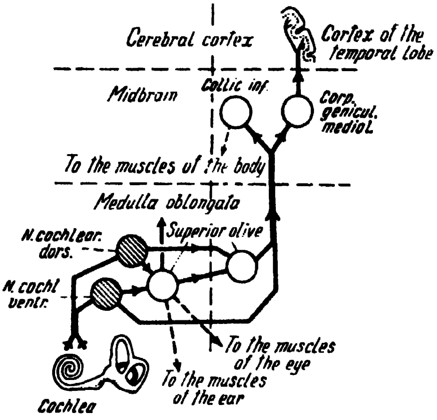

Fig. 317. General diagram of structure of auditory analyser. Only crossed part of auditory fibres is shown.

A large number of nerve fibres runs to the organ of Corti from the *peripheral ganglion of the cochlear nerve* (*ganglion spirale*) situated in the spiral thin duct which passes in the base of the osseous spiral lamina. The spiral ganglion contains about 30,000 bipolar nerve cells. Each nerve cell projects a process which ramifies between the inner and outer acoustic cells. All the nerve fibres extending from the spiral ganglion to the organ of Corti lose their myelin sheath when passing through the opening of the spiral osseous lamina.

Conductive and central divisions of auditory analyser. The peripheral division of the auditory analyser is connected by the auditory nerve through a number of internuncial neurons with the cortical division of the analyser situated in the temporal lobes of the cerebral hemispheres.

The first peripheral neuron, as before stated, is represented in the spiral ganglion in the form of a bipolar nerve cell whose short process runs to the organ of Corti, while the long process enters the auditory nerve. This nerve (the acoustic) contains two kinds of fibres of different physiological significance. One part of the fibres travels to the cochlea forming the cochlear nerve which, properly speaking, must be called the auditory nerve. The other part of the fibres proceeds to the vestibular apparatus (semicircular canals, utriculus and sacculus) and has its own peripheral ganglion—*ganglion vestibulare scarpae*—which lies in the inner auditory meatus. These fibres form the vestibular nerve.

The neurons of the cochlear nerve terminate in two nuclei of the medulla oblongata—*nucleus cochlearis dorsalis* and *nucleus cochlearis ventralis* (Fig. 317). From the nuclei of the medulla oblongata most of the nerve fibres cross to the opposite side, run up to the nuclei of the upper olive as a solid bundle, known as the lateral lemniscus, and reach the midbrain. The remaining nerve fibres do not cross and enter the lateral lemniscus on their own side. The nuclei of the upper olive project short fibres to the nuclei of the motor nerves of the head and body.

In the region of the midbrain some of the fibres of the lateral lemniscus terminate in the inferior colliculus of the corpora quadrigemina; the others, directly in the medial geniculate body of the thalamic region (metathalamus). The medial geniculate bodies are not only an intermediate station for the nervous auditory pathways running to the cortex, but also contain the mechanisms which coordinate the unconditioned auditory reflexes to the muscles of the body. The inferior colliculus of the corpora quadrigemina is also a centre of reflex motor responses to sound. The geniculate bodies and the temporal region of the cortex are connected by nerve fibres which radiate from them (*radiatio acustica*).

From the foregoing scheme it is clear that the entire pathway from the peripheral end of the auditory analyser to the cortex consists at least of three neurons. The first neuron links the organ of Corti with the nuclei of the medulla oblongata; the second, the nuclei of the medulla oblongata with the thalamic region; and the third, the nuclei of the thalamic region with the cortex. The cortical end of the auditory analyser is situated in the upper part of the temporal lobe of the brain, in the region of the sylvian fissure (areas 41 and 42 according to Brodmann). The *temporal gyrus* (Heschl's gyrus) is apparently particularly important.

Conduction of Sound Vibrations in Peripheral Division of Auditory Analyser

Sound vibrations coming into the external auditory meatus are conducted farther through the tympanic membrane and chain of auditory ossicles to the oval window of the middle ear. Microscopic observations show that the amplitude of vibrations of the conic apex of the tympanic membrane usually does not exceed 0.05 mm.; under the action of weak sounds within the limits of audibility the vibrations of the tympanic membrane are not seen in the microscope at all.

The auditory ossicles which form a system of levers and transmit the vibrations of the tympanic membrane of the oval window play an important role in the conduction of sound vibrations (Fig. 318). The whole system of auditory ossicles is suspended in the tympanic cavity by means of ligaments. In addition to the ligaments there are two small muscles: one of them, the *stapedius*, is inserted in the head of the stapes at the point of its joint with the incus; the other, the *tensor tympani*, is inserted in the handle of the malleus. Although the malleus and the incus are connected by a joint, they are so closely bound up that under the action of sound they vibrate as a single unit. These vibrations are conducted to the stapes whose base closes the oval window by means of the annular ligament. The entire sound-conducting system of the middle ear acts like a collector of sound energy, transmitting the latter from the tympanic membrane to the oval window whose surface is 20 times as small as that of the tympanic membrane.

The aforesaid muscles play the role of reflexly acting regulators of the sound-conducting apparatus of the middle ear. Under the action of very strong sounds the contraction of the *tensor tympani* tenses the tympanic membrane, while the contraction of *m. stapedius* retracts the stapes.

The mechanical vibrations of the auditory ossicles are transmitted to the fluid of the vestibule through the base of the stapes in the oval window. Each movement of the stapes in the direction of the vestibule entails a displacement of a certain amount of fluid from the region of the vestibule to the upper canal of the cochlea (*scala vestibuli*). The increase in pressure in the endolymph of the upper canal of the cochlea drives the basilar membrane downward, which presses on the endolymph of the lower canal of the cochlea (*scala tympani*). Since the lower canal of the cochlea communicates with the round window which is closed by a membrane, the latter bulges out in the direction of the tympanic cavity. The vibrations of the auditory ossicles are thus transmitted to the basilar membrane and simultaneously to the hair cells, and excite the endings of the auditory nerve.

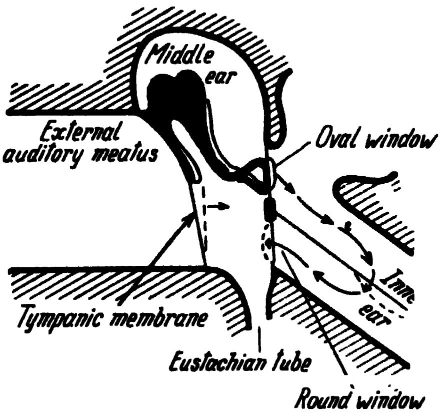

Fig. 318. Sound-conducting apparatus of ear.

Clinical observations show that limitation in the mobility of the auditory ossicles because of their concrescence resulting from inflammatory diseases or a sclerotic process in the region of the oval window markedly impairs hearing. Perforation of the tympanic membrane, however, has but little effect on hearing. Even in the absence of the tympanic membrane, the malleus and incus hearing is retained though considerably weakened. In this case the sound vibrations are, apparently, transmitted to the round window, which, as before stated, is closed by a membrane (the "secondary tympanic membrane") whose vibrations may be conducted to the endolymph and basilar membrane of the cochlea. In this case the so-called *bone conduction* of sound vibrations may play an important role.

Unlike the aforesaid air conduction of sound vibrations, bone conduction is effected directly through the bony tissue of the skull. If the ears are stopped up, i.e., if air conduction is excluded, a vibrating tuning fork with its shank held against the skull, above the mastoid process of the temporal lobe, can be clearly heard. It has been shown that sound waves cause the bones of the skull and the labyrinth to vibrate. The vibration raises the pressure of endolymph in the *scala vestibuli* higher than in the *scala tympani,* since the membrane closing the round window is more elastic than the base of the stapes closing the oval window. As a result, vibrations arise in the basilar membrane and in the hair apparatus, like in air conduction. As regards the action of sound vibrations on the auditory receptor apparatus bone conduction is almost a million times less effective than air conduction.

In medical practice tests of bone conduction are used for diagnostic purposes. In order to compare audibility in air and bone conduction the shank of a vibrating tuning fork is placed against the mastoid process. The moment the vibrations of the tuning fork fade to the extent that the subject no longer perceives the sound through the bone of the skull, the tuning fork is brought close to the auditory meatus. The normal ear still hears the sound for some time. When the sound-conducting apparatus is damaged, air conduction is shortened and bone conduction is lengthened (Rinne's test).

In cases of a unilateral lesion of the sound-conducting apparatus the application of the shank of a vibrating tuning fork to the top of the head is accompanied by a so-called lateralization of sound, i.e., by a relative intensification of sound in the normal ear.

Electric Phenomena in Auditory Analyser

Investigation of the electric phenomena arising in the cochlea, auditory nerve and auditory centres as a result of sound stimulations is very important for the study of the work of the auditory analyser.

Research in electric phenomena in the auditory apparatus made particular headway in the thirties of the current century when, by leading off the potentials from the cochlea of a decerebrate cat (experiments of Wever and Bray) with the aid of an amplifier and a telephone the sound stimulations which had acted upon the ear of the animal were reproduced. The telephone reproduced the nature of the sound vibrations with such exactitude that it was possible to discriminate the pitch of the sound, its timbre and even separate words which were also used for exerting an acoustic influence on the ear of the animal.

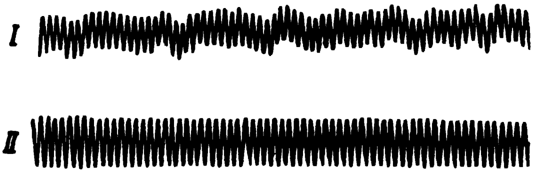

Fig. 319. Oscillogram of cochlear effect (recorded from round window).

I—cochlear effect; II tone of 500 cycles.

The cochlear effect is best observed when potentials from the round window are led off. In this case the potentials may reach the maximum value of about one millivolt. The potentials reproduce the form and frequency of the sound waves in the entire range of frequencies perceived by the ear (Fig. 319). This effect has a very short latent period—less than 0.001 second; it is stable as regards the action of anaesthetizing substances and fatigue, and persists when the cochlea is cooled. Available data allow us to regard the cochlear effect as a physical phenomenon conditioned by the ability of the cochlea to act like a microphone; this phenomenon was therefore named the *microphonic cochlear effect.*

When the electrodes are applied to the auditory nerve or various sections of the auditory pathways, the cerebral cortex included, it is possible to observe bio-electric oscillations connected with the passage of nervous impulses which arise in the receptors of the chochlea under the action of sound stimuli. In their nature and properties they differ from the microphonic cochlear effect, representing the well-known potentials of nervous impulses. Table 31 shows how changes in the conditions under which nervous impulses are conducted—changes due to the inclusion of new neurons on different levels of the central nervous system—increase the latent period and reduce the frequency limit of the nervous impulses reproduced synchronously with the frequency of the acting sound vibrations.

Table 31

Characteristics of Electric Potentials Arising in Various Divisions of Auditory Analyser Under Sound Stimulations

Region from which potentials are led off	Latent period (in m/sec.)	Maximum frequency of nervous impulses reproduced (per sec.)
Auditory nerve	0.9	3,500
Primary auditory centres in medulla oblongata	2.2	2,500
Region of corpora quadrigemina *(colliculus inferior)*	4-5	1,200
Metathalamic region *(corpus geniculatum mediale)*		
Auditory area of cortex	8	100

Sensitivity of Auditory Analyser

Unit of sound intensity. Auditory sensitivity is characterized by a minimum intensity of sound which is sufficient to cause an auditory sensation. The minimum intensity of sound evoking an auditory sensation is designated as the threshold of hearing at the given frequency of sound vibrations. Determination of auditory sensitivity and the threshold of hearing is thus reduced to measuring sound intensity.

The intensity of sound may be defined as the amount of energy which passes in one second over an area of 1 sq. cm. perpendicular to the direction of the sound wave. The intensity of sound can, therefore, be expressed in units of energy—ergs and microwatts.

But the intensity of sound is the square of pressure produced by the sound wave and can, therefore, be characterized by the value of this pressure. Sound pressure is measured in bars, one bar denoting pressure exerted by a force of one dyne on 1 sq. cm. of surface. This value constitutes approximately one-millionth of normal atmospheric pressure.

In present-day acoustics the intensity of sound is usually expressed not in the aforesaid absolute units, but in certain conventional, relative units. For this purpose a certain intensity of sound is taken as a reference unit or level; each given intensity of sound is expressed by a ratio between this sound intensity (J) and the intensity (J_0) taken as a reference standard. The ratio $\frac{J}{J_0}$ expresses the intensity of the given sound relative to a definite reference level.

The value 10^{-16} watt cm.^{2} equalling 10^{-9} erg (cm.^{2}) sec. and corresponding to a sound pressure of 0.000204 bars (at a temperature of 20^0) is taken as the reference level. This value of sound intensity lies somewhat below the lowest threshold of hearing which is observed at the frequency of 1,000 cycles. All intensities of audible sounds encountered in practice will therefore lie above the reference level.

But the range of changes in the intensity of audible sounds is extremely extensive. Suffice it to point out that the threshold of hearing for the extreme low frequencies is 10^9 times the threshold of hearing for the frequency of 1,000 cycles. It is therefore practically more convenient to use not the ratio of sound intensities, but the decimal logarithm of this ratio: $\log_{10} \frac{J}{J_0}$. The logarithmic value of the ratio of two sound energies equalling 1 is taken as a unit of measure and is designated as a "bel." Consequently, one bel corresponds to the ratio $\frac{J}{J_0}$ which equals 10, since in this case $\log_{10} \frac{J}{J_0} = \log_{10} 10 = 1$. But this unit of measure is too large and a unit one-tenth of this, i.e., a *decibel*, is employed in acoustics. Since the number of bels equals $\log_{10} \frac{J}{J_0}$, the number of decibels (N) is 10 times as great, i.e., $N = 10 \log_{10} \frac{J}{J_0}$.

As before stated, the energy of the sound wave is the square of the sound pressure. Hence, the ratio of two different pressures (p and p_0) can be expressed in decibels as follows: $N = 10 \log_{10} \frac{p^2}{p_0^2} = 10 \log_{10} \left(\frac{p}{p_0}\right)^2 = 20 \log_{10} \frac{p}{p_0}$.

If the given sound pressure equals the reference level of intensity, i.e., $p = p_0$, $N = 20 \log_{10} \frac{p}{p_0} = 20 \log_{10} 1 = 0$. Consequently, the reference level of intensity on the scale of decibels is a zero level.

If the sound pressure increases 10-, 100- or 1,000-fold in relation to the zero level, according to the formula $N = 20 \log_{10} \frac{p}{p_0}$, this will correspond to an increase in the intensity of sound by 20, 40 or 60 db; when the sound pressure is doubled, the intensity of sound increases approximately by 6 db (since $\log_{10} 2 = 0.30103$).

The use of the scale of decibels is very convenient as it simplifies computations. The relative intensity of all audible sounds usually does not exceed 120-140 db (Table 32).

Table 32

Intensity of Various Sounds on Scale of Decibels

Sound	Intensity of sound in decibels
Threshold of hearing	0
Faint whisper at a distance of 1.5 m	10
Ticking of a watch	20
Quiet conversation	40
Busy street	70
Shout	80
Fortissimo of a big orchestra	100
Thunder	120

Thresholds of Auditory Sensitivity and Sensations of Pressure

Ascertainment of the level of sound intensity makes it possible to determine the sensitivity of the ear and to express it in certain threshold or minimal values of sound energy which under the given conditions evokes an auditory sensation. Two methods are used for this purpose: the threshold of hearing is determined either by measuring the sound pressure on the tympanic membrane or by measuring the sound intensity in the free acoustic field.

In order to determine the minimum sound pressure which evokes an auditory sensation, a calibrated telephone, a thermophone or some other acoustic radiators are used; they are placed in the direct proximity of the ear or are held close to it. The sound pressure is measured *inside the auditory canal.*

The auditory analyser possesses maximum sensitivity to sounds of 1,000 to 4,000 cycles. Within this range, the ear can perceive sounds with a pressure of less than 0.001 bar. Above and below these frequencies the sensitivity of the ear sharply declines (Fig. 320).

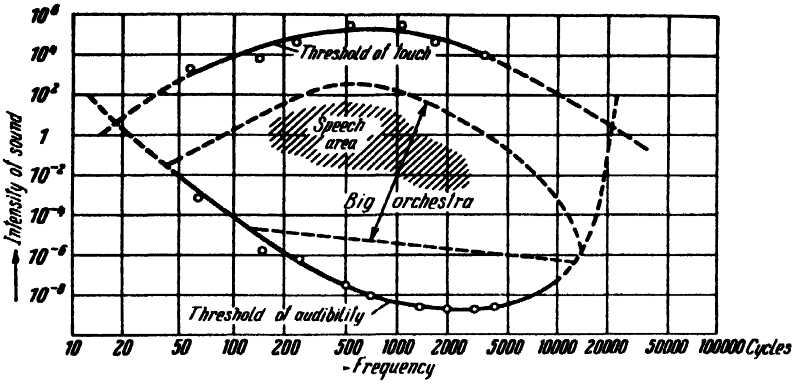

Fig. 320. Threshold of audibility and threshold of touch (pressure) at different frequencies of sound oscillations.

Table 33 shows the threshold value (in bars and millionths of a microwatt) for tones of different frequencies.

Table 33

Threshold Value for Tones of Different Frequencies

Frequency of vibrations	63	128	256	512	1,024	2,048	4,096	8,192	16,384	18,500
Sound pressure (in bars)	0.12	0.031	0.0039	0.0010	0.00052	0.00041	0.00042	0.0025	0.13	4.1
Sound intensity (watts $\times 10^{-12}$)	35	1.06	0.036	0.0024	0.00065	0.00040	0.00042	0.015	41	400,000

The threshold of hearing is usually determined by the second method, i.e., by measuring the sound intensity in the *free acoustic field*, in a room insulated from any external noise or in a special chamber. The source of sound (a telephone) is placed at a distance of 30 to 100 cm. from the ear of the observer. The threshold is determined for the hearing with both ears (binaural threshold) and with one ear (monaural threshold).

It will be observed that the threshold of hearing of the most sensitive ear lies almost on the border of fluctuations of air pressure, i.e., of the fluctuations in absolute auditory rest and are evoked only by the disorderly thermal movement of air molecules.

The aforesaid thresholds characterize the degree of sensitivity of the auditory analyser to the minimum intensity of sound of different frequency. The thresholds of maximum sound intensity can also be determined. If the sound is gradually intensified, a peculiar sensation of pressure arises in the ear at a definite level of intensity and with further intensification of the sound becomes painful.

The level of sound intensity at which an auditory sensation passes into a sensation of pressure determines the threshold of maximum sound intensity, or the upper absolute threshold of auditory sensitivity. This threshold is called the threshold of ***pressure sensation*** (Fig. 320). The nature of this sensation depends on the frequency of sound and on the individual peculiarities of the person perceiving the sound. At low frequencies vibrations superposed on the sound are distinctly felt. In some cases giddiness is observed probably due to the stimulation of the semicircular canals. High sounds may evoke a sensation which is similar to acute pain.

If we express the threshold of pressure sensation in bars, it will equal approximately 1,000 bars, which corresponds to the pressure of 1 gr. on 1 sq. cm.; it is thus very close to the threshold of cutaneous pressure sensation.

Between the threshold of hearing and the threshold of pressure sensation lies the *range of audibility;* within it come all the sounds of various intensities and frequencies perceived by the auditory analyser.

The results of testing the hearing ability are graphically represented in so-called *audiograms.* An audiogram is plotted in the form of a curve, the frequencies being marked along the abscissae and the hearing loss in decibels—along the ordinates.

With age auditory sensitivity greatly declines. The age alterations of hearing pertain mainly to tones of high frequency, namely, those exceeding 1,000 cycles; sensitivity to tones of low frequency hardly changes.

Differential Thresholds of Frequency and Intensity of Sound

An auditory sensation, called the pitch of the tone, corresponds to a given frequency of sound vibrations. Tones of high frequency are usually called high tones, while tones of low frequency are designated as low tones. Two tones are used to determine just perceptible changes in the sensation of the frequency of a tone; the tones are sounded alternately, the frequency of one gradually incrasing from unison to the moment when the observer begins to distinguish a just perceptible difference between the two tones.

The differential threshold of frequency (pitch) reaches its maximum value within the range of low frequencies and with sounds of low intensity. In frequencies ranging from 500 to 3,000 cycles, the value of the differential threshold changes very little and constitutes approximately 0.003. This means that within this range of frequencies it is possible to discriminate a change in frequency equalling 3 cycles per 1,000 cycles. Individuals possessing a highly developed sense of hearing can distinguish a tone of 1,000 cycles from that of 1,001 cycles.

The following question arises: how long must a sound last to enable the ear to perceive its pitch? It has been found that for tones lying within the middle region of the frequency range the minimum duration required is 0.01 second. For tones below 200 cycles 3 or 4 sound waves are required to enable the ear to perceive the pitch of the tone; for tones of about 1,000 cycles, 12 sound waves; and for tones of 10,000 cycles and over, 250 sound waves.

A certain degree or strength of auditory sensation called the *loudness* of the sound corresponds to the physical intensity of the sound. The correlations between the loudness of the sound and its intensity are quite complicated; it is therefore absolutely wrong to identify these essentially different ideas. The loudness of the sound is a function not only of the intensity of the sound, but also of its frequency. Two sounds having the same intensity but differing in frequency are not equally loud.

Studies of the differential threshold of sound intensity have shown that the minimum perceptible increase is not a constant value but depends on the initial intensity of the sound. The value of the relative increase in intensity is greatest when the sounds are weakest (at the threshold of hearing); with the increase in the intensity of sound it diminishes and, finally, from 40 db it remains constant. This dependence of the ratio $\frac{\Delta J}{J}$ on the initial sound intensity does not agree with the laws of Weber and Fechner.

On the basis of the results obtained from the determination of differential auditory sensitivity it is possible to establish the total number of simple tones of various frequencies and pitches which can be differentiated by the human auditory analyser. For sounds of medium intensity—if the frequency alone changes—there are about 1,500 just perceptible degrees of modifications, from the lowest audible frequency to the highest. If the intensity of the tone alone changes, there are about 325 just perceptible degrees of loudness in the middle portion of the range of frequencies. The total number of discriminable tones for the entire range of audibility is tremendous—about 340,000.

Adaptation and Fatigue of Hearing

Auditory sensitivity varies with the action of a sound. It declines when a tone of sufficient intensity or duration is sounded and increases in complete or relative silence. This physiological phenomenon of adaptation of sensitivity to different levels of sound intensity is called *adaptation of hearing*. When the ear is adapted to silence the sound perceived appears much louder than when heard for a long time. In the latter case the sound appears weakened or deadened.

When the sounding of a tone ceases recovery of auditory sensitivity, i.e., adaptation to silence, is observed. Complete recovery arises very quickly—in 10 to 15 seconds. The nature of adaptation varies with the frequency of the sounding tone. A decline of loudness is observed predominantly for tones close to the sounding tone.

Auditory sensitivity alters in both ears, even if the sound acts only on one ear; this means that it alters in the auditory centres.

The process of adaptation is thus a phenomenon caused by corresponding changes in the functional state of both the peripheral and central divisions of the sound analyser.

When the acoustic stimulus acts for a long time (for example, for several hours) auditory sensitivity declines more because of the excessive stimulation of the auditory apparatus; unlike adaptation, it persists for a longer time after the acoustic stimulus ceases to act. This protracted decrease in the sensitivity of the ear caused by its long functioning may be defined as fatigue. The symptoms of fatigue disappear under adequate conditions, for example, in relatively noiseless surroundings. Normal auditory sensitivity is never fully recovered if the auditory analyser is systematically subjected to the fatigue-producing action of a sound for a very long time (months and years). Such acoustic trauma results in degenerative changes in the cells of the organ of Corti and in the nervous elements of the inner ear accompanied by a considerable decline of hearing. It is responsible for the professionally impaired hearing or deafness which develop after many years of work in noisy shops of industrial enterprises.

Masking

The suppression of one tone when another tone is sounded is called *masking.* This phenomenon can be easily observed in everyday life when a weak sound becomes less audible as a result of the simultaneous action of loud sounds. The effect of masking manifests itself in the rise of the threshold of the masked sound. This rise of the threshold, or the intensity of suppression, differs for tones of various frequencies. For tones whose frequency is below the frequency of the masking tone, the rise of the threshold is insignificant (except the neighbouring tones): it equals 1 or 2 db. Tones which lie above them are masked very highly: the intensity of their masking is close to the level of the masking tone. The tones whose frequency is close to that of the masking tone are masked most. For example, a masking tone of 800 cycles greatly obscures the tones of 700, 900 and 1,000 cycles.

The masking influence of various noises is observed in everyday life. Measurements taken in city public places show that the extent of masking reaches 30 db and more.

Sound Localization

Man and the higher animals can judge the direction of a sound and to localize the source of a sound in space. The direction of a sound is correctly judged with both ears, owing to which this ability is called the *binaural effect.* The ability to judge the direction of a sound depends on two factors: first, on the difference in sound intensity in both ears owing to their different distance from the source of sound, and, second, on the phase difference or, to be exact, on the interval between equal phases of sound waves entering the two ears.

The importance of the intensity factor for judging the direction of the sound can be easily illustrated by a simple experiment. If two tones of different intensity are directed separately to both ears, the listener will locate the sound in the direction of the stronger tone. This is the apparent direction of the sound. It occurs in everyday life. The ear which is turned towards the source of sound perceives a stronger sound than the other ear, since the latter is partly screened by the head which is in the way of the sound wave propagation.

The extent of screening is determined by the relation between the size of the screen and the length of the sound wave. As before stated, the wavelength of audible sounds ranges from several centimetres to several metres. The longer the wave, the less pronounced the screening, since the sound wave makes a detour. For low tones the difference in sound intensity in the right and left ears is so negligible that it is not sensed at all. The intensity difference for high tones is quite perceptible. For frequencies above 5,000 cycles this difference may reach 30 db. Hence, the ability to judge the direction only of high tones is accounted for by the difference of sound intensity in both ears. Practice shows, however, that the human ear can also judge well the direction of low tones.

As regards low tones it is possible that the ability to judge their direction depends on the difference in the time the equal phases of the sound wave arrive at both ears. Special experiments demonstrated that if two sounds of equal intensity were brought to both ears the judgement of the direction was determined by the phase difference.

Practice also shows that the ability to judge the direction of the sound by the difference in the time the equal phases arrive at both ears is lost if the sound wave is shorter than double the distance between the ears. For example, the length of the sound wave of a tone of 700 cycles equals 48 cm. It is possible to judge the direction of this sound by the phase difference. It is difficult to judge the direction of a tone of 800 cycles, whose wavelength is 42.5 cm., only by the phase difference; for higher tones such judgement becomes altogether impossible.

Thus the direction of low tones can be judged by the phase difference. the direction of high tones—by the intensity difference.

The auditory analyser can judge not only the direction of the sound, but also the distance of its source. The distance is judged by an estimation of the sound intensity, which is possible only if the intensity and timbre of the given sound were already differentiated by the listener before. Differentiation of the sound source requires joint activity of both hemispheres. After transection of the *corpus callosum* in the dog it was impossible to elaborate a differentiation to the sound source (a whistle with 1,500 vibrations per second) (K. Bykov).

Normally judgement of the direction of a sound and the distance of its source is a very complex process in which each of the aforesaid factors plays an essential role. It will be observed that in judging the direction of the sound (especially in the vertical plane) the shape of the head and of the auricles is also very important. The latter are, apparently, important in locating the source of the sound situated behind or in front of the head. The movement of the head, or the displacement of the body in the direction of the source of sound is another factor which greatly facilitates judgement of its direction. The importance of the joint activity of a number of analysers in judging the direction of a compound sound under natural conditions is evident from the fact that persons deaf on one ear learn to judge the direction of sounds if they repeatedly differentiated the nature of the sounds.

Sound-locators used in warfare for locating various sources of sound in the air and in the water (airplanes, guns, submarines, etc.) are based on the principle of the binaural phasic effect.

Resonance Theory of Hearing

Of all the existing theories of hearing the *resonance theory*, advanced by Helmholtz in 1863, is the most substantiated and agrees with the clinical and experimental data.

On the basis of the structural features of the cochlea Helmholtz assumed that the fibres of the basilar membrane of the cochlea were set into sympathetic vibration by the sounding tone according to the principle of resonance.

We know from the description of the fine structure of the cochlea that the basilar membrane is approximately 3 to 4 times as narrow at the base of the cochlea as it is at the apex (0.16 mm. at the base and 0.52 mm. at the apex). Thus the transverse fibres of the basilar membrane, which number about 24,000, gradually grow longer from the base to the apex. The fibres of the basilar membrane are very loosely connected, but are stretched by the spiral ligament. The latter is more developed in the lower spirals of the cochlea, which warrants the assumption that here the tension of the transverse fibres of the basilar membrane is greater.

According to Helmholtz's resonance theory, each of these fibres is, like a string, tuned to a definite tone, to which it resounds. In reality, however, not one but several fibres always vibrate, the number of vibrating fibres being the greater the stronger the sound. The number of sympathetically vibrating fibres is smallest at the threshold of sound intensity. The sound-receiving elements of the cochlea are so disposed that high tones are perceived at its base and low tones at its apex. This conception of the receptor properties of the cochlea is supported by numerous experimental and clinical facts.

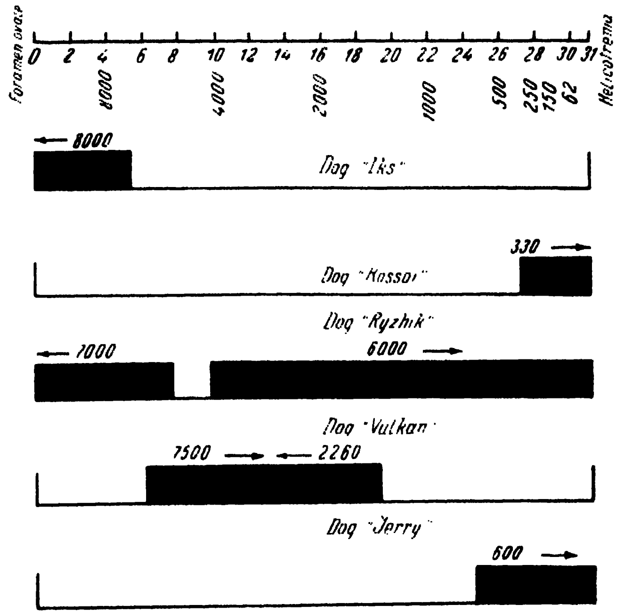

Fig. 321. The nature of disorders of hearing resulting from partial lesion in cochlea.

Figure schematically shows unfolded basilar membrane of cochlea as horizontal lines with black bands plotted on them according to frequency tones lost after injury to cochlea. Top—linear scale (in mm.) of basilar membrane indicating frequencies perceived by its separate parts. In dog Iks cochlea was destroyed in region of main cochlear spiral; in dogs Kossoi and Jerry, in region of upper cochlear spiral; and in the dog Vulkan, in region of middle cochlear spiral (after L. Andreyev).

Studies of histological and functional changes in the cochlea resulting from unduly long-continued action of sounds of different intensities and frequencies on the receptor apparatus, show that the degenerative and functional changes are localized in the organ of Corti by the frequency of the injurious sound. Protracted action of highfrequency sounds produces changes in the lower spirals of the cochlea; action of low-frequency sounds, in the region of its apex.

Helmholtz's theory was substantiated by L. Andreyev's experiments; using the method of conditioned reflexes, he established with considerable precision the nature of the functional disturbances of hearing resulting from a partial lesion of the cochlea.

The experiments were performed on dogs in which alimentary (salivary) conditioned reflexes had been elaborated to pure acoustic tones from 50 cycles and over to the upper limit of hearing, and to various noises. Complete destruction of the cochlea on one side did not affect the conditioned reflex reactions of the animals. A subsequent partial lesion of the cochlea on the other side showed that the nature of the resulting changes in hearing depended on the location of the lesion. The closer the lesion to the base of the organ of Corti, the higher the frequency of the tones to which the conditioned reaction disappears and, contrariwise, the closer to the apex of the cochlea, the lower the frequency of the tones. Thus a local lesion of the cochlea causes a disturbance of its function only as regards a definite group of frequencies, while the intact part of the cochlea retains its ability to react to sound stimuli of corresponding frequencies; at the same time the ability to differentiate sounds according to their pitch is also retained (Fig. 321).

Experimental data obtained by other methods agree with these results. It has been established, for example, that the electric response of the cochlea to high-pitched or low-pitched tones considerably declines depending on the location of the lesion in the cochlea.

Clinical observations of patients with various hearing defects also provide valuable material which testifies that tones are perceived according to their frequency at optimal zones of the basilar membrane. Of great interest in this respect are the results of histological studies of the inner ear in deceased patients whose hearing had been examined during their life and its defects were well known. A rather strict conformity was established between the site of the lesion and the frequency of the tones to which they had been completely or partly deaf.

But Helmholtz's resonance theory meets with some objections. It is difficult, for example, to explain by this theory the tremendous range (from 20 to 20,000 cycles) of perceivable tones of different frequencies. This phenomenon can be explained only if we assume that the elasticity of the different parts of the basilar membrane varies tremendously. The resonance theory also meets with difficulties in explaining the binaural effect which manifests itself in judging the direction of the sound.

In order to eliminate the aforesaid difficulties some additions to the resonance theory have been made. It is assumed that under the action of a tone not only the fibres which resound to the given frequency vibrate, but also other fibres of the basilar membrane and the cochlear fluid. The maxima of the resonance are distributed along the basilar membrane according to the frequency of the exciting tone, while the sensation of the tone is determined by the site of the maximal amplitude of vibrations of the basilar membrane. In this form the resonance theory meets with fewer objections from the point of view of the physics of the inner ear.

PART XV

VOICE AND SPEECH

CHAPTER 72

VOICE

Of all the stimuli acting upon the auditory analyser of man some of the most important are the articulate sounds which constitute speech. There is no doubt that the development of speech has greatly contributed to perfecting the work of the auditory analyser. The ability to produce sounds is connected with the existence of a special vocal apparatus. While speech is inherent only in man, many animals also possess vocal apparatuses.

The human vocal apparatus consists of the larynx with its vocal cords which are set into vibration by currents of air emitted from the lungs. The cavities situated higher—the pharyngeal, oral and nasal—play the part of resonators which amplify separate overtones of the sounds that are produced and thereby determine the timbre peculiar to individual voices. Voice is produced not so much by the vibrations of the vocal cords, as by the condensation and rarefaction of the column of air, caused by these vibrations, mainly above the vocal cords.

Unlike reed wind-instruments where a column of air is caused to vibrate by the vibrations of an elastic reed in the direction of the current of air, i.e., the longitudinal direction, the vocal cords vibrate mainly in the direction transverse to the current of air. While in a reed wind-instrument the frequency of vibrations is determined by the length of the tube and the reed, in the larynx the pitch of the tone depends on the length and tension of the vocal cords and on the strength of the blast of the air. Besides, the vocal cords produce sound under the action not only of expiratory, but also of inspiratory currents of air.

Structure and Function of Vocal Apparatus

The skeleton of the larynx is formed by a number of cartilages connected by joints and ligaments. They include first of all: the thyroid cartilage, the cricoid cartilage and the two arytenoid cartilages. The thyroid cartilage, the largest in the larynx, consists of two plates joined together in front at an angle. The posterior margin of each plate forms two processes—the superior and inferior cornua of which the second articulates with the cricoid cartilage situated lower. The latter has the shape of a ring and passes posteriorly into a broad plate. By its two inferior articulate surfaces the cricoid cartilage articulates with the inferior cornua of the thyroid cartilage, while the articulate surfaces on the corners of the upper margin of the plate join with the articulate surfaces of the arytenoid cartilages lying above. The bases of the arytenoid cartilages are located on the upper margin of the plate of the cricoid cartilage. At the base of the arytenoid cartilage lies the vocal process which is directed towards the cavity of the larynx and to which the *ligamentum vocale* is attached; here also is the muscular process which is extended outwards.

The epiglottis situated in front of the upper opening of the larynx is a valve which closes the entrance to the larynx and prevents food and saliva from getting into it. The cavity of the larynx is lined by a mucous membrane.

The true vocal cords (*ligg. vocalia vera*) are two symmetrically situated folds of the mucous membrane of the larynx containing elastic fibres. Anteriorly they are attached to the angle of the thyroid cartilage and posteriorly to the vocal processes of the arytenoid cartilage. The medial, free margins of both vocal cords protrude into the larynx as pointed edges, which form the glottis (*rima glottidis*). A vocal and a respiratory part are distinguished in the glottis. The vocal part is represented by the anterior section of the glottis enclosed within the vocal cords. The respiratory part is considerably shorter; it is bounded by the medial surface of the vocal processes of the arytenoid cartilages. It looks like a hollow in the posterior part of the glottis. It is usually open, inspiration and expiration being freely effected through it even when the glottis is closed.

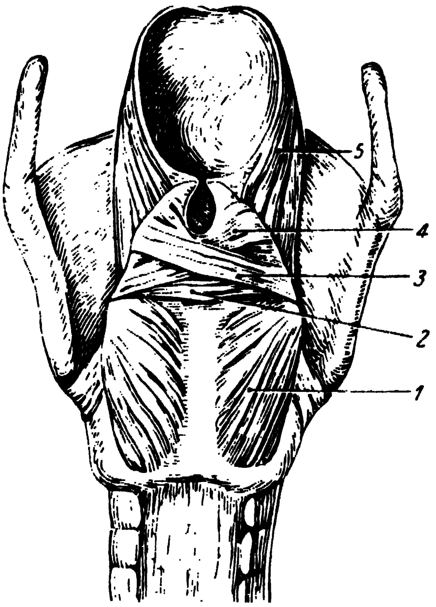

Fig. 322. Muscles of larynx (posterior view).
1—posterior cricoarytenoid muscle; *2*—transverse arytenoid muscle; *3* and *4*—oblique arytenoid muscles; *5*—aryepiglottic muscle.

Above the true vocal cords are the less distinct false vocal cords (*ligg. vocalia spuria*). These cords take no part in the production of voice. Between the true and false vocal cords, on the lateral wall of the larynx there is a pocket-shaped recess—the laryngeal ventricle (*ventriculus laryngis*) which in some animals is a highly resounding cavity.

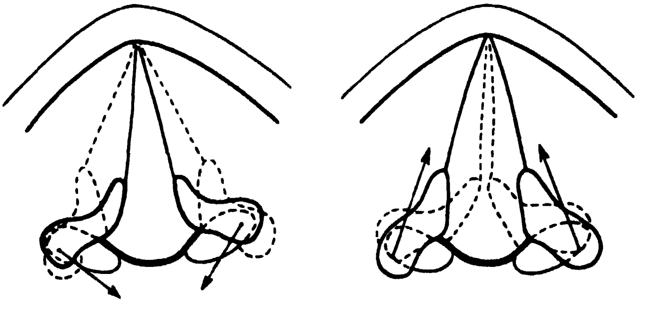

Fig. 323. Action of cricoarytenoid muscles—posterior (left) and lateral (right).
Horizontal section of arytenoid cartilages: during quiet respiration (solid line) and during contraction of these muscles (dotted line). Direction of tractive force is indicated by arrows.

Changes in the position and tension of the vocal cords are due to the displacement of the movable cartilages of the larynx caused by contraction of definite muscles (Fig. 322). If, for example, the thyroid cartilage turns forwards on the horizontal axis which passes through the cricothyroid joints the anterior point of attachment of the vocal cords moves away from the posterior point and the vocal cords lengthen and tense. When the arytenoid cartilages come closer or move away from each other, or when each of them turns on its vertical axis, which is connected with a displacement of the vocal processes, the aperture of the glottis is respectively narrowed or widened (Fig. 323).

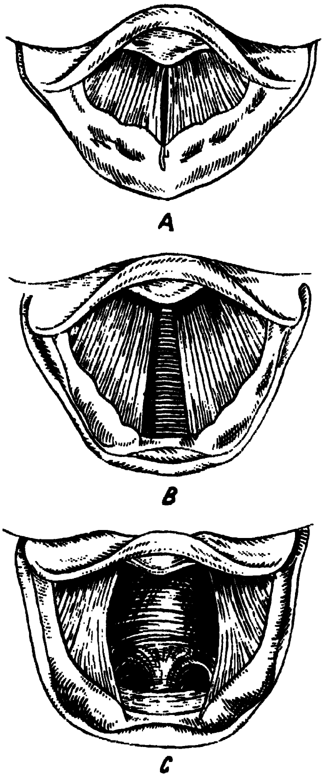

Fig. 324. Laryngoscopic views of glottis.
A—during production of high note in singing; B—in normal inspiration; C—in very deep inspiration.

Contraction of the symmetric cricothyroid muscles tenses the vocal cords. Contraction of the thyroarytenoid muscle relaxes the vocal cords. Contraction of the posterior cricoarytenoid muscles widens the opening of the glottis, while contraction of the lateral cricoarytenoid, thyroarytenoid, transversal arytenoid and oblique arytenoid muscles causes the glottis to narrow (Fig. 322).

The movements of the vocal cords can be directly observed with a laryngoscope—a small round mirror fastened to a handle at a 45^0 angle. The back of the mirror is brought to the posterior wall of the pharynx, while the tongue is kept out of the way. Using a concave mirror fixed on his forehead, the observer directs a light reflected from an external source onto the laryngoscope to light the vocal cords. The vocal cords thus reflected by the laryngoscope can be seen by the observer.

Laryngoscopic examination shows that during quiet respiration the glottis has the form of a triangle (Fig. 324). In deep respiration it considerably dilates exposing the bifurcation of the trachea. When a sound is uttered the free edges of the vocal cords tense and come so close together that only a narrow cleft between them is left. At this time the vibration of the free edges of the vocal cords can be observed.

Innervation of Vocal Apparatus

The larynx is innervated by the sympathetic nerve and by two branches of the vagus—the superior laryngeal, predominantly afferent, and the inferior laryngeal, exclusively efferent (motor) nerve. Only the cricothyroid muscles are innervated by the superior laryngeal nerve; all the other muscles of the larynx, by the inferior laryngeal nerve.

Transection of the inferior laryngeal nerves paralyzes the vocal apparatus and results in the loss of voice. Transection of the superior laryngeal nerves only modifies the voice. But since this excludes all the afferent innervation of the laryngeal mucous membrane and since, therefore, defensive reflex movements can no longer be effected (lowering of the epiglottis, closure of the glottis, coughing), foreign substances (food, saliva) may penetrate into the trachea and bronchi and thus cause pneumonia and death.

The vocal apparatus is under the control of the cerebral cortex. Cortical impulses both start and regulate it. But the delicate control of the laryngeal muscles particularly manifest in the acts of singing and speech is impossible without the afferent impulses from the receptor formations contained in the muscles, tendons and ligaments of the vocal apparatus. In this case, as in other receptor systems, the cerebral cortex performs a certain analysing function owing to which the *speech motor analyser* may be regarded as a particular form of activity of the motor analyser. The cortical nucleus of this analyser is situated in the region of the second and third frontal convolutions. The possibility of unconditioned reflex manifestations of the vocal reactions, for example, in pain, indicates the existence of subcortical centres of vocal reaction; these centres, however, are under the control of the cerebral cortex which can inhibit the manifestation of such reactions.

Characteristic Features of Human Voice

The scale of frequencies reproduced by human voices ranges from 80 to 1,024 cycles. The individual voice encompasses about two octaves, i.e., the ratio between the extreme frequencies is approximately 1 : 4. In some cases the compass of an individual voice may be of four octaves. It may be observed by way of comparison that the piano has 7 octaves and the organ 8 octaves.

According to the pitch of phonation the following *vocal registers* are distinguished: bass (80 to 341 cycles), tenor (128 to 518 cycles), alto (170 to 683 cycles) and soprano (246 to 1,024 cycles). The vocal register is determined principally by the length of the vocal cords. Women's vocal cords are shorter than men's (15 to 18 mm. against 20 to 24 mm.) and their voices, therefore, have a higher pitch than those of men. In boys the size of the larynx considerably increases at puberty, owing to which the voice passes to a lower register.

Variations in the pitch of the sound are produced by changes in the tension of the vocal cords, in the length of their vibrating part and in the pressure of the air which passes through the glottis. The vibrating part of the vocal cords is shortened because the cords approach each other to the point of contact in the posterior part of the glottis, as a result of which only the anterior part of the vocal cords continues to vibrate. The higher the pitch of the sound, the tenser the vocal cords, the shorter their vibrating part and the higher the pressure of the air in the larynx. Observations show that when a tone of medium intensity and frequency is produced, the air pressure in the trachea reaches 230 mm. H_2O. The intensity of the sound is approximately proportional to the force of the blast of expired air.

CHAPTER 73

SPEECH

Speech is a specific human function which developed in the process of collective labour as a means of intercourse; it is indissolubly connected with the development of abstract thinking.

Peripheral Apparatus of Speech

The peripheral apparatus of speech is the aforesaid vocal apparatus of the larynx with the cavities of the pharynx, mouth and nose situated above it. The laryngeal sound-producing apparatus alone is not enough to produce all the sounds which constitute articulate speech. The vocal cords of the larynx can only produce sounds of different pitch, but of the same timbre. But speech is characterized by complex variations in the timbre of the sounds produced by the larynx. These variations are produced in the cavities of the pharynx, mouth and nose.

Speech is composed of "vowels" and "consonants." The vowels are tonal sounds, while the consonants are predominantly noise sounds.

The vowels are formed as follows: in addition to the fundamental frequency the compound sound, produced by the vibrations of the vocal cords, contains a large number of overtones whose frequency exceeds the fundamental frequency 2, 3, 4, 5 and more times. The formation of overtones is due to the fact that the vocal cords, like strings, vibrate not only by their entire length, thus producing the fundamental tone, but also by their smaller parts—halves, thirds, fourths, etc. The amplitude of these partial vibrations steadily decreases while their frequency increases (inversely proportional to the length of the vibrating part). As before stated, it is the overtones which impart the timbre to a voice.

The laryngeal sound, rich in overtones, is essentially modified in the cavities of the pharynx and mouth. These cavities play the role of resonators which can be tuned to different frequencies of vibrations, since their form and size can considerably vary, especially because of the changes in the position of the tongue and lips. Differently resounding cavities amplify the corresponding overtones and these modifications of the laryngeal sound determine the distinctions between different vowels.

Thus, owing to the resonance properties of the cavities lying above, a sound arising in the larynx acquires the features of a definite vowel. In other words, the component parts of the vowels are overtones of the fundamental tone produced by the vocal cords (Helmholtz).

X-ray pictures of the oral cavity taken during the pronunciation of the vowels a, e, i, o, u show in each case a different position of the tongue and a resulting difference in the form and size of the resounding cavities. Oscillographic records of sound vibrations produced by pronouncing vowels show both the fundamental tone and the higher overtones.

In contrast with vowels which are tonal sounds, in the formation of consonants an essential role is played by noise sounds arising in the cavities of the pharynx, mouth and (in some cases) the nose. The following groups of sounds are distinguished in the phonation of consonants depending on the degree of participation of the vocal cords (voice): 1) semivowels—such as l, m, n, r, in which voice predominates over noise and which by their nature come close to vowels; 2) voiced consonants—such as b, d, g, v, z, etc.—the formation of which, in addition to noise, also involves the voice; 3) voiceless consonants—such as p, f, t, s, k, etc., produced by noise sounds without the participation of the voice.

The noise components of the consonants arise as a result of friction of the stream of air when it passes through the narrowed part of the oral cavity—the fricative consonants—or as a result of the abrupt opening of the closed oral cavity—the explosive consonants. The fricative consonants (Lat. *fricare*—to rub) include the sounds produced by the passage of a stream of air through the slit formed as a result of the approximation of the tongue to the upper teeth (d, t), to the hard palate (z, r), and to the soft palate (g, k), and through the opening formed by the lips (v, f), or teeth (s) when they are brought together. The explosive consonants include the sounds which arise when the lips are abruptly opened (b, p).

Whispered speech does not involve the vocal cords, i.e., it consists exclusively of noise sounds. To whisper vowel or consonant sounds the cavities of the mouth, nose and pharynx assume the same position as when these sounds are pronounced aloud. The passing stream of air (both expired and inspired) produces corresponding sounds by its friction against the walls of the aforesaid cavities. In this case there are no tones.

Central Speech Apparatus

The activity of the peripheral speech apparatus is fully controlled by the cerebral cortex: it proceeds exclusively under the influence of cortical impulses. This testifies to the existence not only of efferent (motor) innervation of the various parts of the speech apparatus (respiratory musculature, muscles of the larynx, pharynx, organs and walls of the oral cavity), but also of fine afferent signalization effected by various parts of this apparatus through the medium of sensory structures situated in the muscles, tendons and ligaments. The delicate analysing activity of the corresponding cortical centres is possible only in the presence of such afferent signalization, which Pavlov called *kinesthetic*. The two-way innervation connection between the cerebral cortex and the various parts of the peripheral speech apparatus is effected by a number of cranial nerves.

Speech, as a specific human function, which arises simultaneously with man's ability of abstract thinking, is in some measure connected with the activity of the entire cerebral cortex. At the same time clinical observations show that certain pathological disturbances of speech are due to lesion of definite parts of the cortex. There are, for example, two forms of aphasia (loss of the power of speech)—motor and sensory. Motor aphasia manifests itself in the inability to coordinate the work of the muscles of the speech apparatus, which is indispensable for the pronunciation of words, although the motor innervation of these muscles taken separately is intact. This disorder of speech is usually due to a lesion of the cortex in the region of the second and third frontal convolutions (Broca's area, see Fig. 280, *I*). Sensory aphasia (word deafness) manifests itself in the fact that the patient hears spoken words but is unable to understand them; this means that the connection between the word as a conditioned stimulus with the stimuli signalized by it has been lost. This speech disturbance is usually observed in lesions of the cortex in the region of the superior temporal convolution (Wernicke's area, see Fig. 280, *II*).

These facts show that separate sections of the cerebral cortex possess specific features as regards speech.

Speech as External Manifestation of Second Signalling System

Pavlov regarded speech as the external manifestation of the second signalling system which interacts with the first signalling system (Chapter 65).

Defining speech from the physiological point of view as the "signal of signals," Pavlov did not confine the second signalling system to speech activity alone. He connected this activity with generalization and abstraction, with the "specifically human, higher mentality." Thus, according to Pavlov, the second signalling system represents a direct and inseparable interconnection of speech and thinking activity. The origin and development of abstract thinking and speech are historically connected with the social production activity of men, with the social conditions of human society.

The abstraction of verbal signals from concrete stimuli is facilitated by the formation of complex chains from combinations of verbal stimuli, since a considerable part of verbal signals are elaborated in adults not because of a combination with the direct action of external or internal agents, but because of a combination with the previously elaborated verbal designations. The complex chains of abstracted verbal designations may consist of a large number of links, but the initial link is indispensably connected with the action of concrete agents upon the first signalling system.

Of exceptional importance for the study of the second signalling system is Pavlov's following statement concerning the unity of the fundamental laws of activity of the first and second signalling systems: "...it cannot be doubted that the fundamental laws governing the activity of the first signalling system must also govern that of the second, because it, too, is activity of the same nervous tissue."*

Indeed, the study of the origin and development of children's speech shows that the development of the second signalling system in a child proceeds according to the laws of formation of cortical temporary connections (N. Krasnogorsky, A. Ivanov-Smolensky, K. Bykov et al.).

From the second half of the first year of life, when conditioned reflexes and differentiations of the first signalling system begin to be formed in children, they manifest initial speech noises which become gradually differentiated into speech sounds and syllables. By the end of the first year the child begins to combine separate syllables into simplest words. The first speech reactions rapidly acquire properties of conditioned stimuli. By the end of the first year the child already speaks 4 or 5 words.

In the child's normal verbal intercourse with the surrounding people verbal connections are formed by way of imitation (through the medium of auditory and visual stimuli) and are fixed by repetition. After the verbal connections have become fixed external and internal stimulations of the first signalling system begin to evoke speech reactions.

The second year is a period of rapid development of the child's speech activity. The stock of words increases; it includes from 200 to 400 words, reproduced by the child in the form of binomial and trinomial combinations. At the same time the grammatical system of speech begins to take shape. In the second year of life the child shows the first signs of abstract thinking expressed in the transformation of words from simple stimuli into "signal of signals."

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* I. Pavlov, *Complete Works*, Vol. III, Book 2, p. 336.

Transformation of a word from a simple acoustic stimulus of the first signalling system into a "signal of signals" with the property of an element of the second signalling system requires the formation and accumulation of a sufficient number of conditioned connections with the given word.

Of interest in this respect are the results of observations carried out on children of the age of one year and eight months (M. Koltsova). Conditioned connections to the word "doll" were elaborated in two groups of such children: three conditioned connections with a large number of reinforcements (about 620) were elaborated in one group and 30 conditioned connections with much fewer reinforcements (about 120) in the other group. Subsequently both groups of children were subjected to the following test: each child was told to collect all the dolls by picking them out of a large number of various toys. The children of the first group failed: they either picked out the single doll which had always been used in the experiment, or collected all the toys indiscriminately. To them the word "doll" was either a simple conditioned signal, or a primitively generalized signal without any adequate differentiation of stimuli. The children of the second group collected all the dolls differentiating them from the remaining toys; to them the word "doll" had already become a "signal of signals" with the property of a generalizing stimulus.

If the number of conditioned connections elaborated to the given word is increased and the foregoing test is repeated, the following fact clearly manifests itself: the word becomes a generalizing stimulus after elaboration of 15 to 20 conditioned connections to it. As a large number of conditioned connections is formed the latent period of the reactions diminishes and the reaction itself becomes more stable and rapid.

Thus, an increase in the number of conditioned connections elaborated to a conditioned signal is a physiological condition indispensable for the conversion of this signal into a "signal of signals." This also pertains to the formation of the meaning of each word.

Pavlov's theory of the second signalling system crowns his entire creative scientific work. By disclosing the physiological principles of speech (language) and thinking he laid a firm materialist foundation for a natural-scientific elaboration not only of the physiology of the brain, but also of such branches of science as psychology and psychiatry. Here, too, the underlying guiding principle is Pavlov's postulate concerning the unity of the fundamental laws of activity of the first and second signalling systems.

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